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Implications of somatosensory amplification for the design of chronic pain clinical trials

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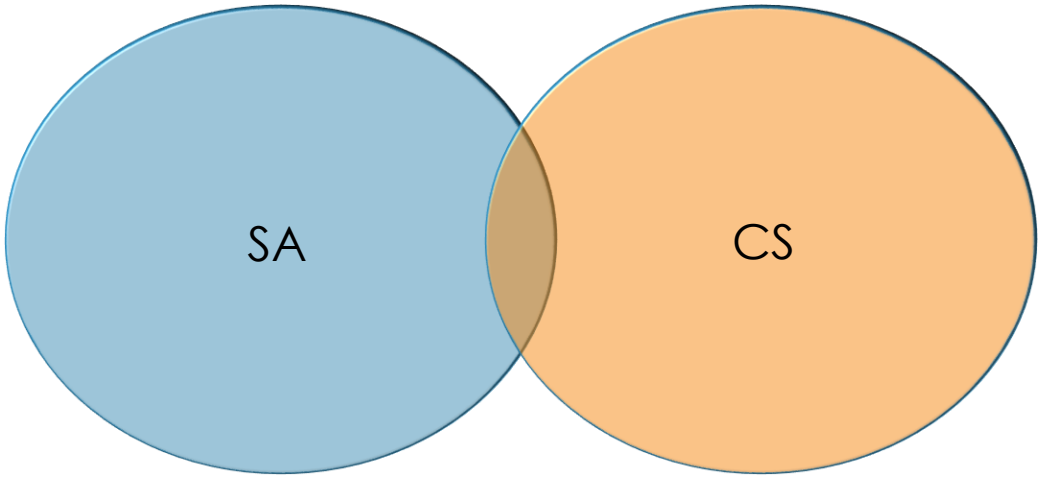
Terms/Implications

- Is there a distinction? (different labels for the same process?)
- Are the terms useful?
- Does it matter?
  - Is there value in disentangling general sensitivity/physical/pain specific/psychological issues?
- How do we measure one vs. the other?
- If one improves – will the rest get better too?

- What are the implications for clinical trials?
  - Patient samples
  - Baseline measures (stratify?)/measure throughout trial?
  - Outcome measures

Somatosensory Amplification vs. Central Sensitization

- Overlap?



Sensory Amplification vs. Central Sensitization

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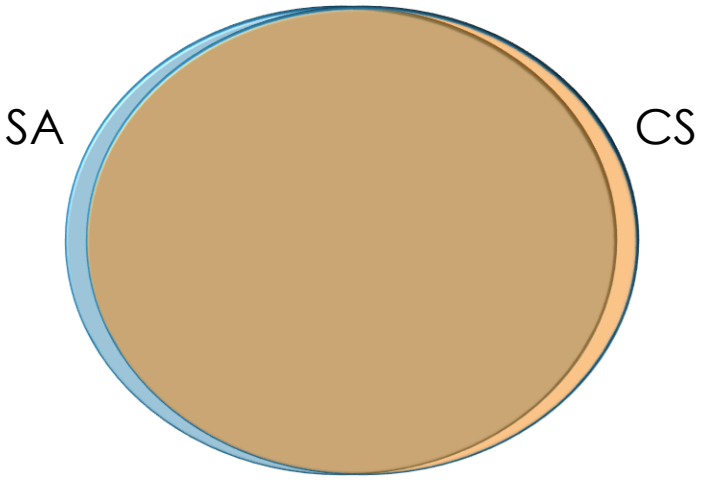

Definitions

- Central Sensitization
- Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. (IASP taxonomy)
- Not "related" to cognitive or emotional factors.

- Somatosensory Amplification
  - No IASP definition
  - *Somatosensory* refers to information about the body per se including visceral organs, rather than information about the external world (e.g., vision, hearing, or olfaction).
  - **Somatosensory amplification (SA)** is a tendency to perceive normal somatic and visceral sensations as being relatively intense, disturbing and noxious. Sensitization also implies that it is an active process that results from various stimuli, eg, trauma. On the other hand, the term sensitivity is a clinical manifestation of sensitization, exemplified by sensitivity or amplification response to various nociceptive, nonnociceptive, and environmental stimuli . (Yunus 2008)
  - "Somatosensory amplification appears to refer to the intensification of perceived external and internal threats to the integrity of the body ("somatic threat amplification") rather than amplification of perceived or actual bodily events only." (Köteles & Witthöft, 2017)
  - Central somatosensory nervous system**
  - Peripheral somatosensory nervous system

'Heightened awareness of and attention to internal sensations and symptoms'

Somatosensory Amplification vs. Central Sensitization

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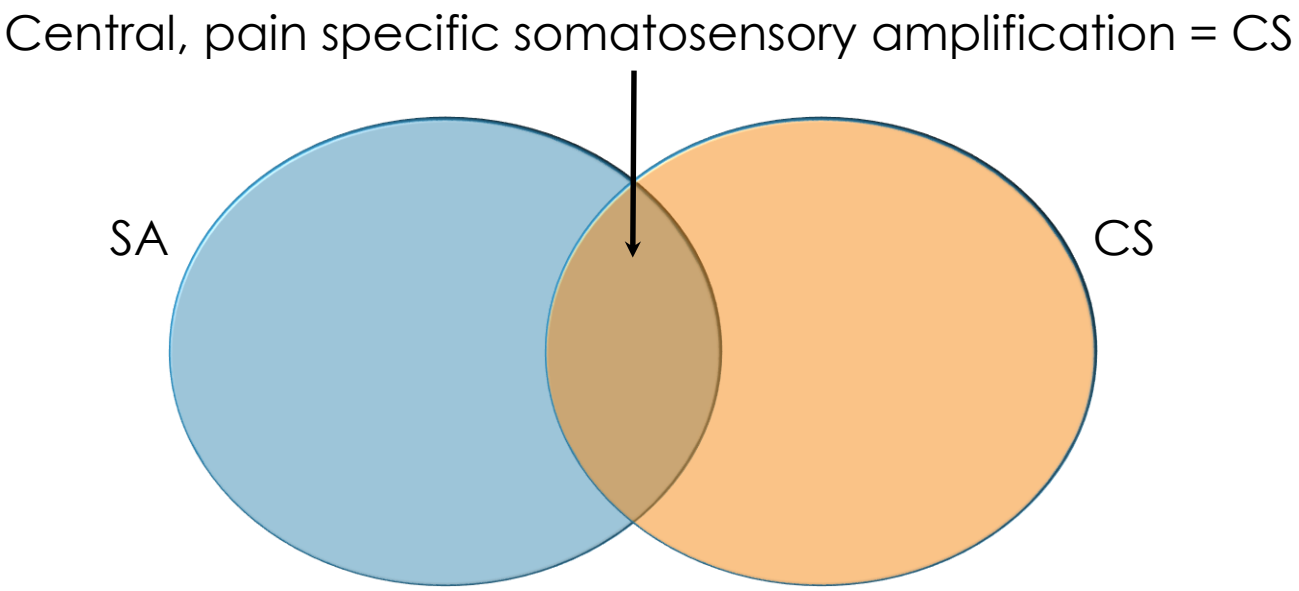

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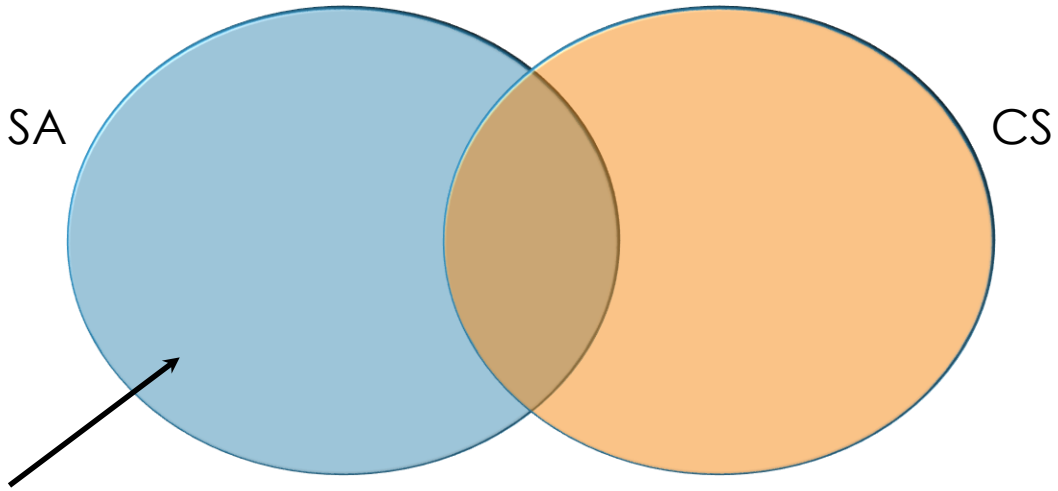


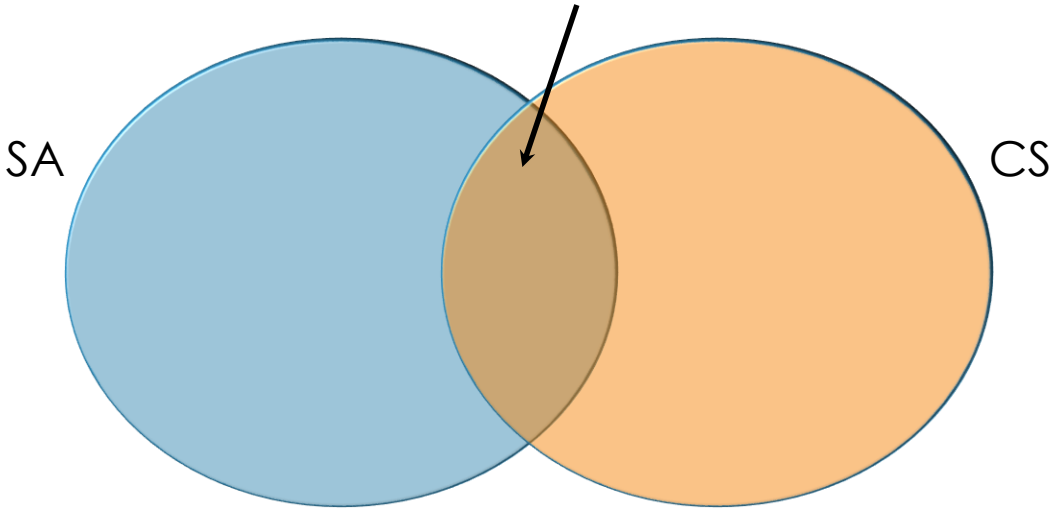
SSAS is associated with objective physiological measurements like EEG (Nakao et al., 2007)

Somatosensory Amplification vs. Central Sensitization

- Overlap?

Sensory Responsiveness Questionnaire associated with PNP

(Weissman-Fogel et al., 2018)



Sensory Processing Sensitivity (>2K; include pain ~40)

Sensory over-responsiveness; Sensory alteration;
Somatic awareness, Anxious arousal, Somatic arousal

How are GS and CS related?

Systematic Review

What Are the Predictors of Altered Central Pain Modulation in Chronic Musculoskeletal Pain Populations? A Systematic Review

Jacqui Clark, MSc[1,2,3], Jo Nijs, PhD[2,3], Gillian Yeowell, PhD[1], and Peter Charles Goodwin, PhD[1]

Conclusions: Premorbid and acute stage high sensory sensitivity and/or somatization are the strongest predictors of altered central pain modulation in chronic musculoskeletal pain to date. This is

2017

SSA/GSS

- Factor Analysis
- Chronic Pelvic Pain (n=424), mixed pain (n=200) and healthy folks (n=415)
- 18 Somatic Awareness subscale of the Complex Medical Symptom Inventory
- 4 sensory items from the Sensory Sensitivity subscale
- Sleep (PROMIS)
- Depression (HADS)

Schrepf et al., 2018 (Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network)

GSS

- **Factor 1:**
  - Broad amplification/ awareness of sensory processes
  - Both somatosensory (internal) and external
- **Factor 2:**
  - Severity of clinical pain
  - Nonspecific CNS symptoms

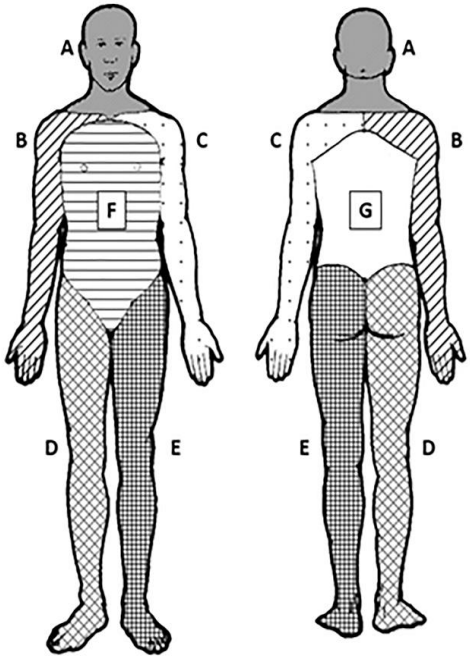
Measure	Factor 1	Factor 2
Number of pain sites	**0.547**	0.152
Somatic Awareness	**0.820**	0.006
Sensory Sensitivity	**0.702**	-0.046
Fatigue	0.005	**0.802**
Sleep Disturbance	0.012	**0.640**
Depressive Symptoms	-0.169	**0.852**
Cognitive Dysfunction	0.009	**0.599**
Pain Severity	-0.067	**0.468**
Factor Correlation:	**.633**	

Schrepf et al., 2018

GSS

- Brief General Sensory Sensitivity Screen

The body map below is divided into seven regions. Please check each region where you have experienced pain during the last week.



A: Head, neck
B: Right shoulder, arm, hand
C: Left shoulder, arm, hand
D: Right hip, leg, foot
E: Left hip, leg, foot
F: Chest, abdomen
G: Back

Please read the following list of symptoms. If you have had any of these symptoms for at least three (3) months in the past year, please mark the appropriate box.

Dry mouth	❑
Rapid heart rate	❑
Problems with balance	❑
Sensitivity to certain chemicals, such as perfumes, laundry detergents, gasoline and others	❑
Sensitivity to sound	❑
Frequent sensitivity to bright lights	❑

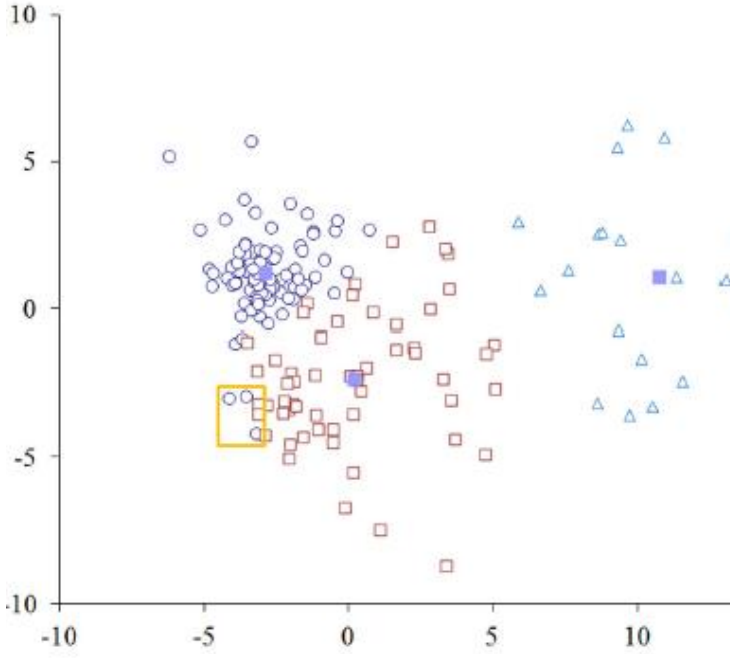
Schrepf et al., 2018

Profiling

Subgrouping of rheumatoid arthritis patients based on pain, fatigue, inflammation and psychosocial factors

Yvonne C. Lee, MD, MMSc[1], Michelle L. Frits, BA[1], Christine K. Iannaccone, MPH[1], Michael E. Weinblatt, MD[1], Nancy A. Shadick, MD, MPH[1], David A. Williams, PhD[2], and Jing Cui, MD, PhD[1]

Mostly fatigue and catastrophizing



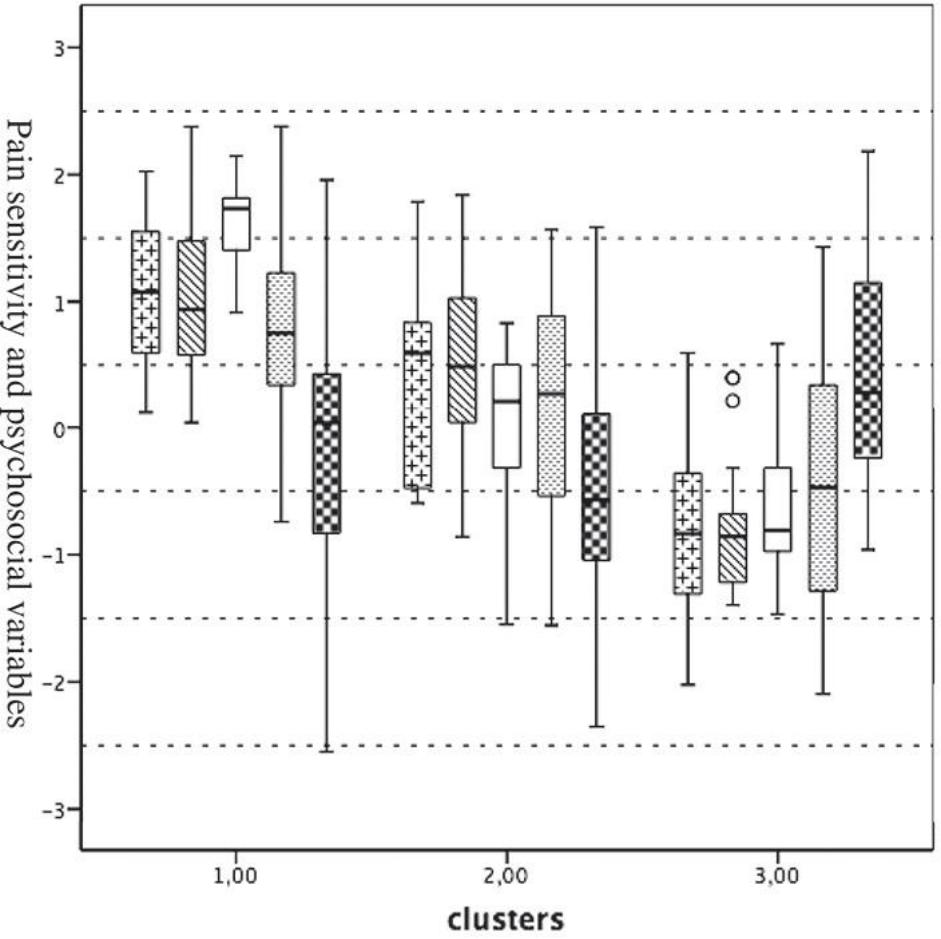
Mostly swollen joint count

- Cluster 1 Lowest pain, swollen counts and psych issues
- Cluster 2 Lower objective findings, higher WPI and more psych issues
- Cluster 3 Higher objective findings, moderate/high psych issues
- Center

Characteristic	Cluster 1 (N = 89)	Cluster 2 (N = 57)	Cluster 3 (N = 23)	*P*-value[b]
Swollen joint count	0.0 (0.0–1.0)	2.0 (0.0–4.0) [c]	12.0 (10.0–14.0) [d,e]	<0.0001
BPI pain intensity	3.0 (2.0–4.0)	3.0 (2.0–5.0) [c]	3.0 (2.0–5.0)	0.03
Fatigue	20.0 (10.0–30.0)	70.0 (50.0–80.0) [c]	60.0 (25.0–80.0) [d]	<0.0001
Sleep problems	27.2 (16.1–41.1)	38.3 (27.2–46.7) [c]	35.6 (17.5–47.8)	0.009
HADS Depression	3.0 (1.0–5.0)	4.0 (1.0–7.0) [c]	5.0 (2.0–8.0) [d]	0.004
Illness burden	1.0 (0.0–3.0)	2.0 (1.0–3.0) [c]	1.0 (0.0–2.0) [e]	0.06
Catastrophizing	6.0 (1.0–12.0)	12.0 (5.0–21.0) [c]	9.0 (3.0–18.0)	<0.0001

Lee et al., 2014

Profiling (general sensitivity)



Cluster subgroups based on overall pressure pain sensitivity and psychosocial factors in chronic musculoskeletal pain: Differences in clinical outcomes

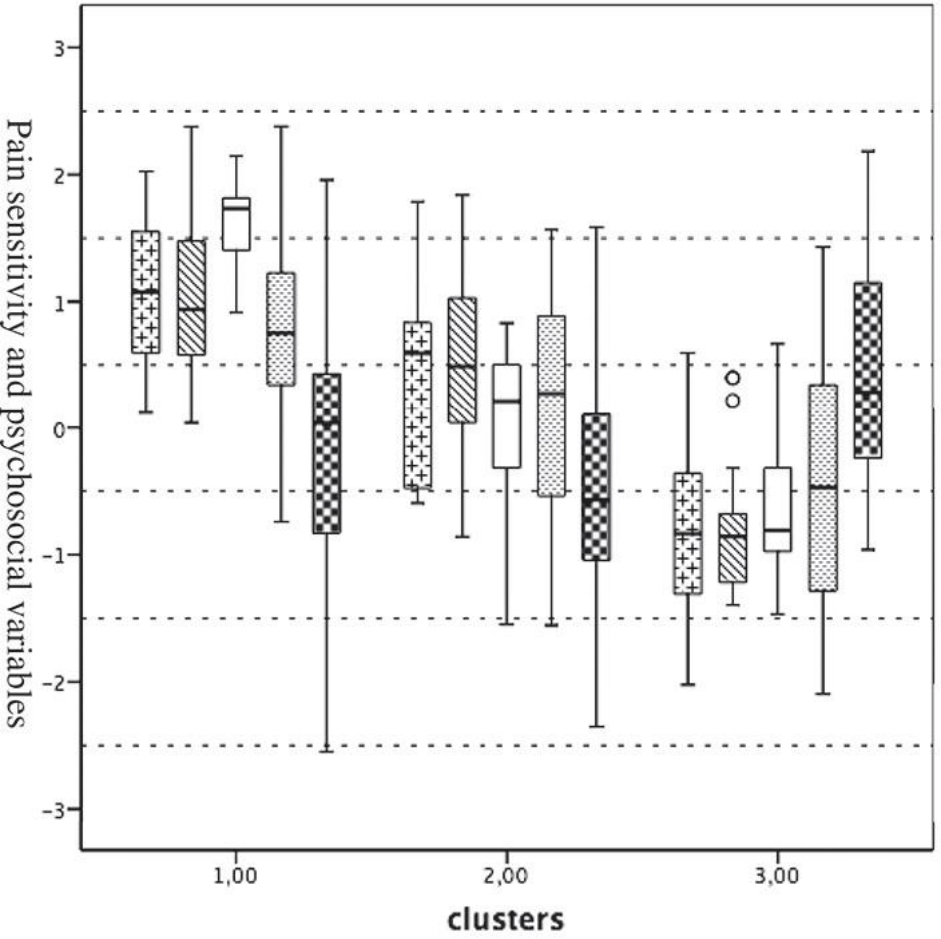
Suzana C Almeida, Steven Z George, Raquel D. V Leite, Anamaria S Oliveira & Thais C Chaves

Cluster 1: High pain sensitivity and high psychosocial distress (n=12)
Cluster 2: High pain sensitivity and intermediate psychosocial distress (n=39)
Cluster 3: Low pain sensitivity and low psychosocial distress (n=29)

PPT anatomical sites
Anterior cervical
Upper trapezius
Second rib
Lateral epicondyle
Knee joint interline
Suboccipital muscle
Supraspinatus muscle
Greater trochanter
Gluteal
Thenar site

Almeida et al., 2018

Profiling (general sensitivity)



More pain and disability

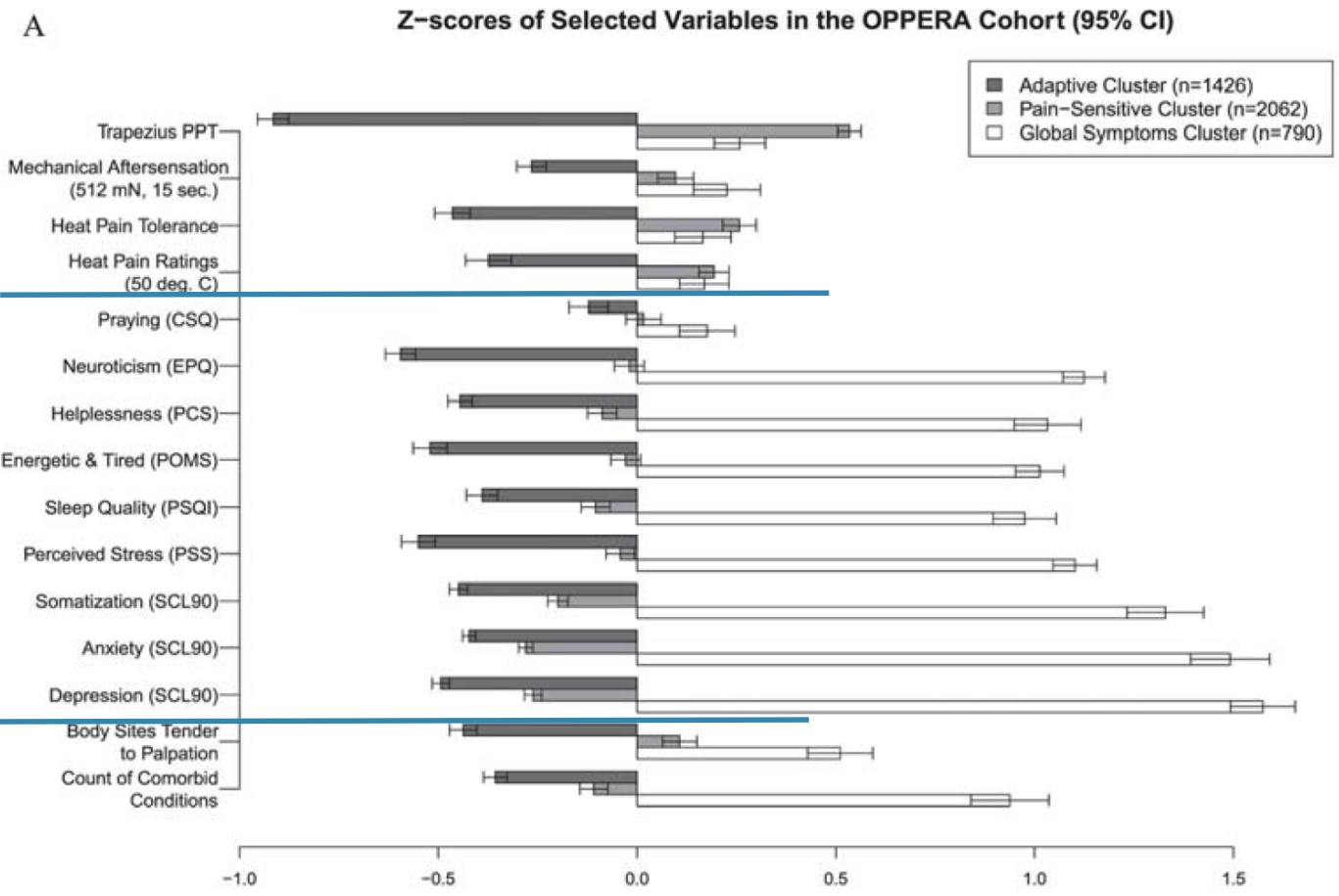
Cluster 1: High pain sensitivity and high psychosocial distress (n=12)
Cluster 2: High pain sensitivity and intermediate psychosocial distress (n=39)
Cluster 3: Low pain sensitivity and low psychosocial distress (n=29)

Almeida et al., 2018

Profiling

Identification of clusters of individuals relevant to temporomandibular disorders and other chronic pain conditions: the OPPERA study

Eric Bair[a,b,c,*], Sheila Gaynor[d], Gary D. Slade[a,e,f], Richard Ohrbach[g], Roger B. Fillingim[h], Joel D. Greenspan[i], Ronald Dubner[i], Shad B. Smith[a,c], Luda Diatchenko[j], and William Maixner[a,c]



Global Symptoms: vastly increased risk and severity of pain and physical/mental dysfunction

Pain-Sensitive: greater sensitivity to exp pain, slightly more psych distress

2017

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- Implications:
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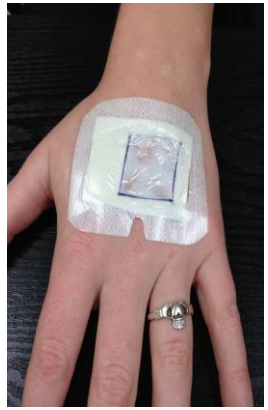
I was here first!
Pain / Somatosensory Amplification + Psychobehavioral Distress
Clinical Pain
©2012 Simon Griffiths

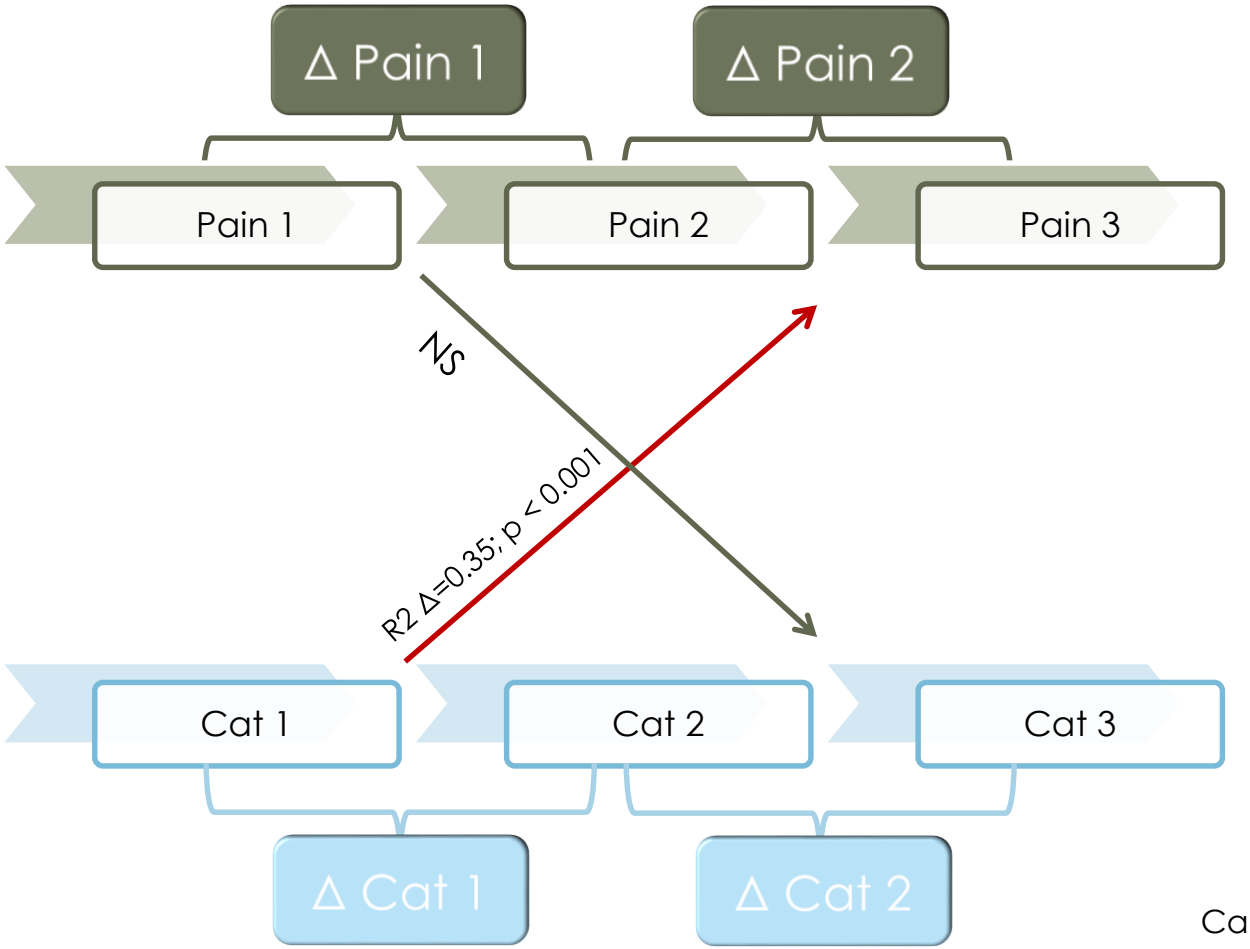
Chicken or egg?

- Psychobehavioral factors contribute to the risk of developing pain and likely aid in maintaining it.
- OPPERA and other studies *postoperative models* suggest pain amplification is a risk factor for developing pain.
- Other studies have challenged this and might suggest pain amplification plays a role in maintenance.
  - *Modify and perpetuate*

Catastrophizing Proceeds Pain

- Cross-Lagged Panel Design





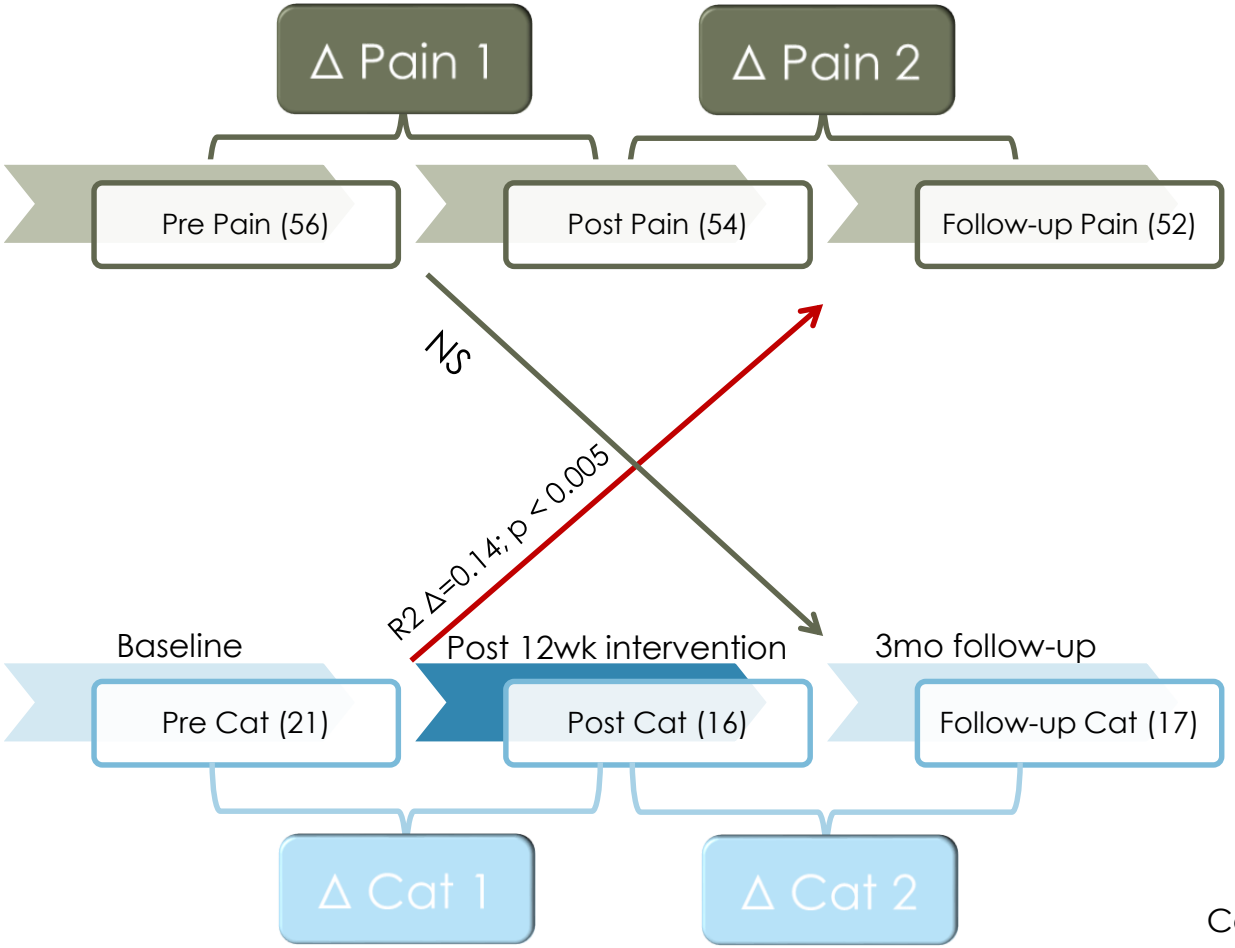
Campbell et al., 2010

Chicken and eggs?

- Regardless, seems like there is (or maybe are?) common pathway(s)…
- If you treat pain, will the other symptoms improve?

Reduced Catastrophizing Proceeds Reduction in Pain

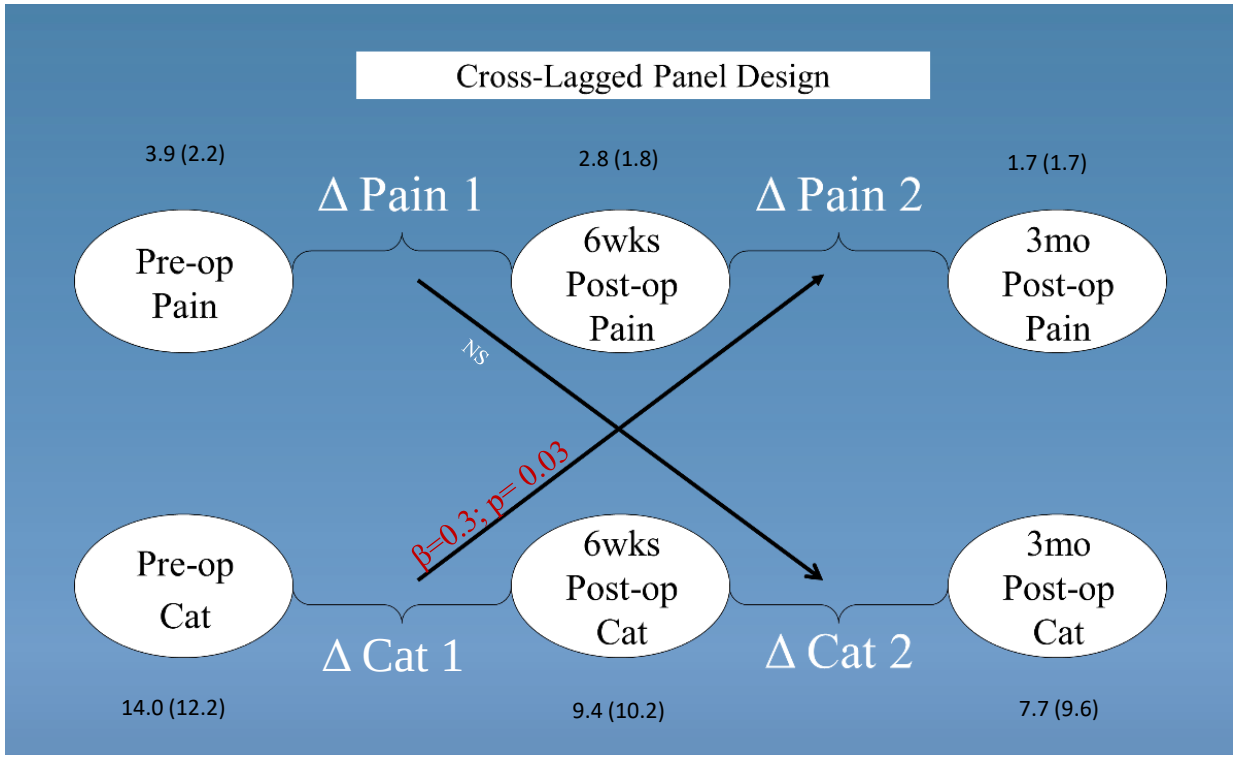
- FM patients in an exercise clinical trial *



Campbell et al., 2012

Chicken or egg?

- Reductions in pain catastrophizing proceed reductions in pain following TKR.



Variables	PCS (BL)	PCS (6wks Post)	PCS (3mo Post)
BPI (BL)	.52**	.09	.17
BPI (6wks Post)	.33**	.50**	.31**
BPI (3mo Post)	.28**	.40**	.43**

Speed et al., in prep

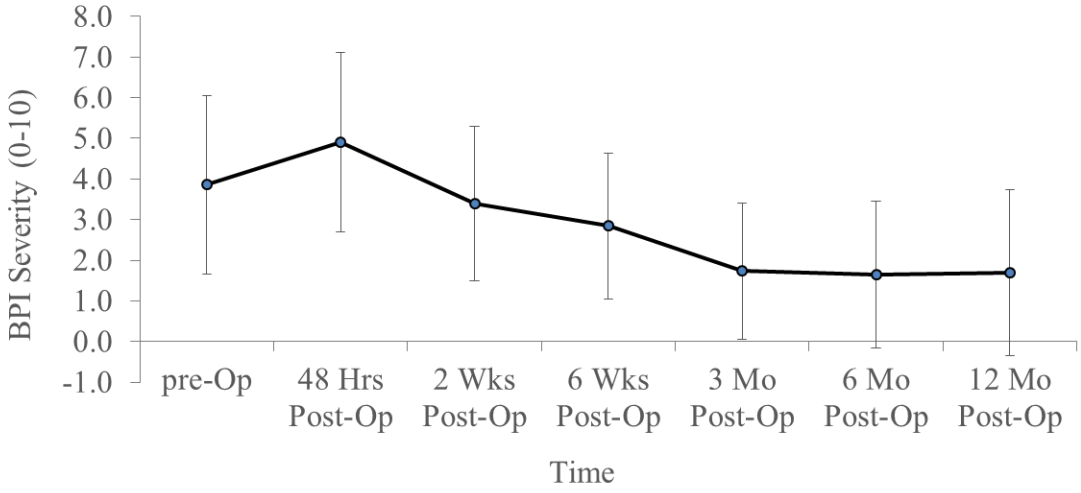
TKA Study: Harvard/Hopkins

Demographics	Mean (SD) or % (n)
Sex (% women)	60% (144)
Race/Ethnicity (%NHW)	88% (211)
Age	65.0 (8.2)

*

pre-Op | 48 Hrs Post-Op | 2 Wks Post-Op | 6 Wks Post-Op | 3 Mo Post-Op | 6 Mo Post-Op | 12 Mo Post-Op

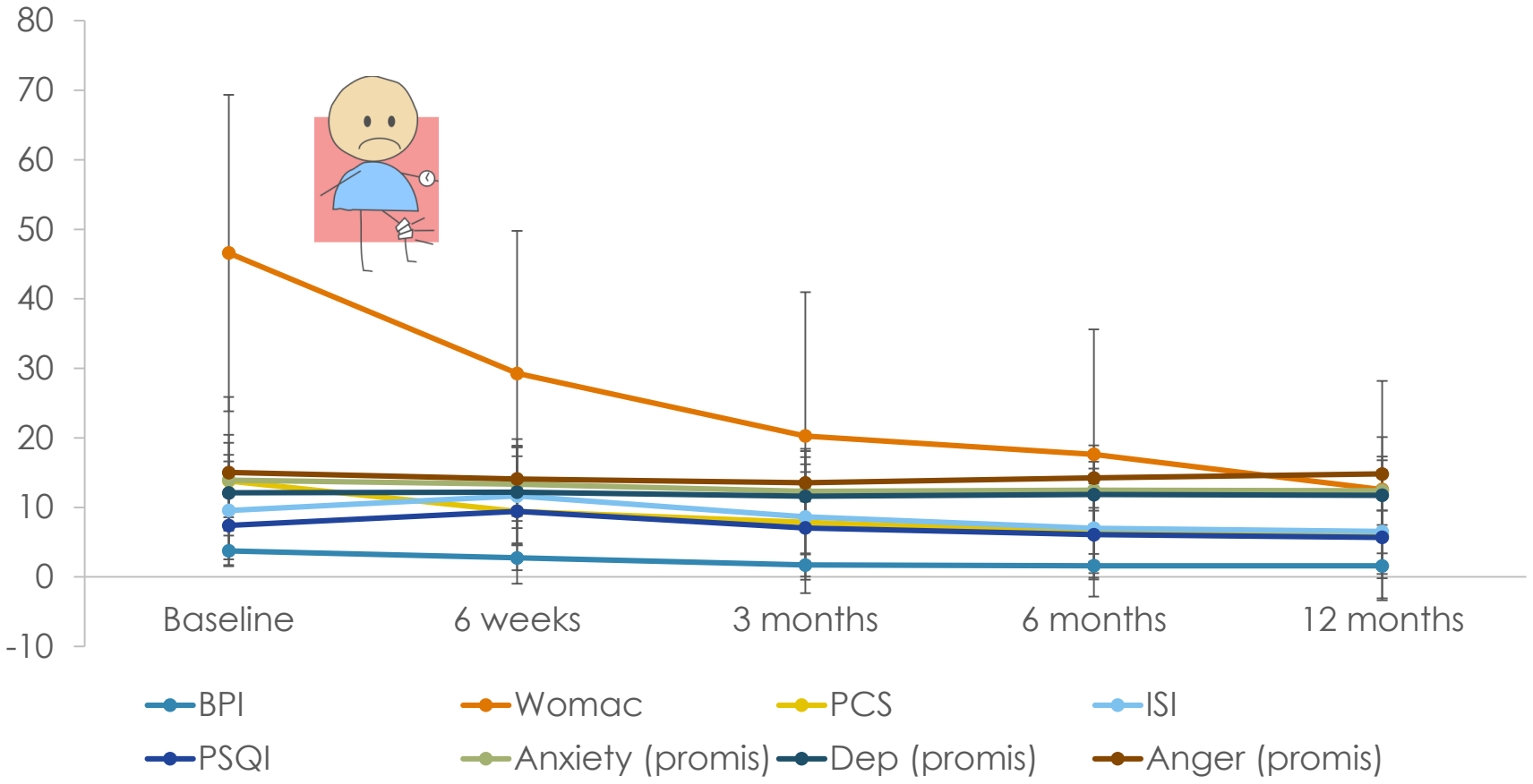
TKA Study: Harvard/Hopkins



12mo ~25% pain ≥ BL

What improves when pain improves?

Pain, Function and Psychobehavioral Factors following TKR



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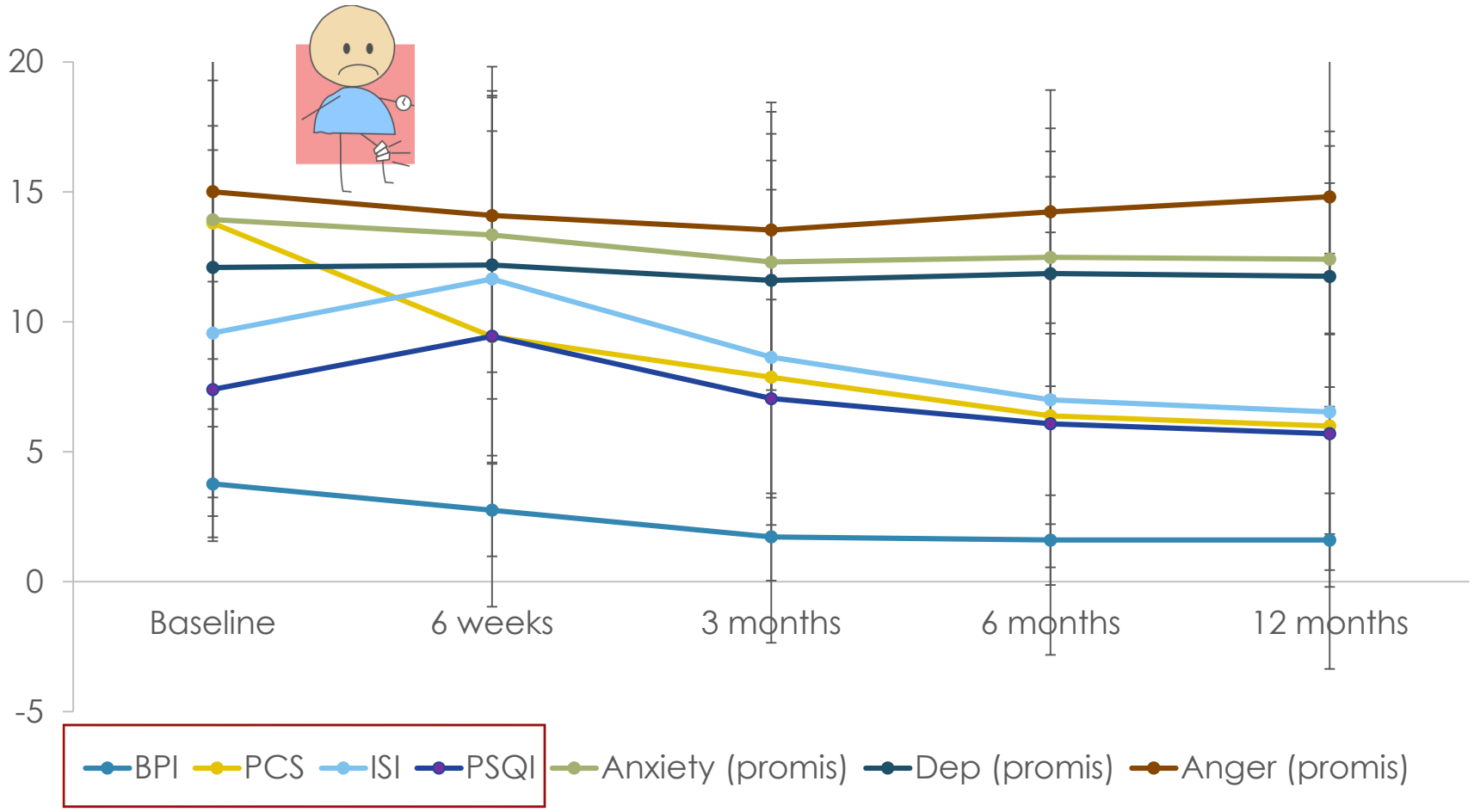
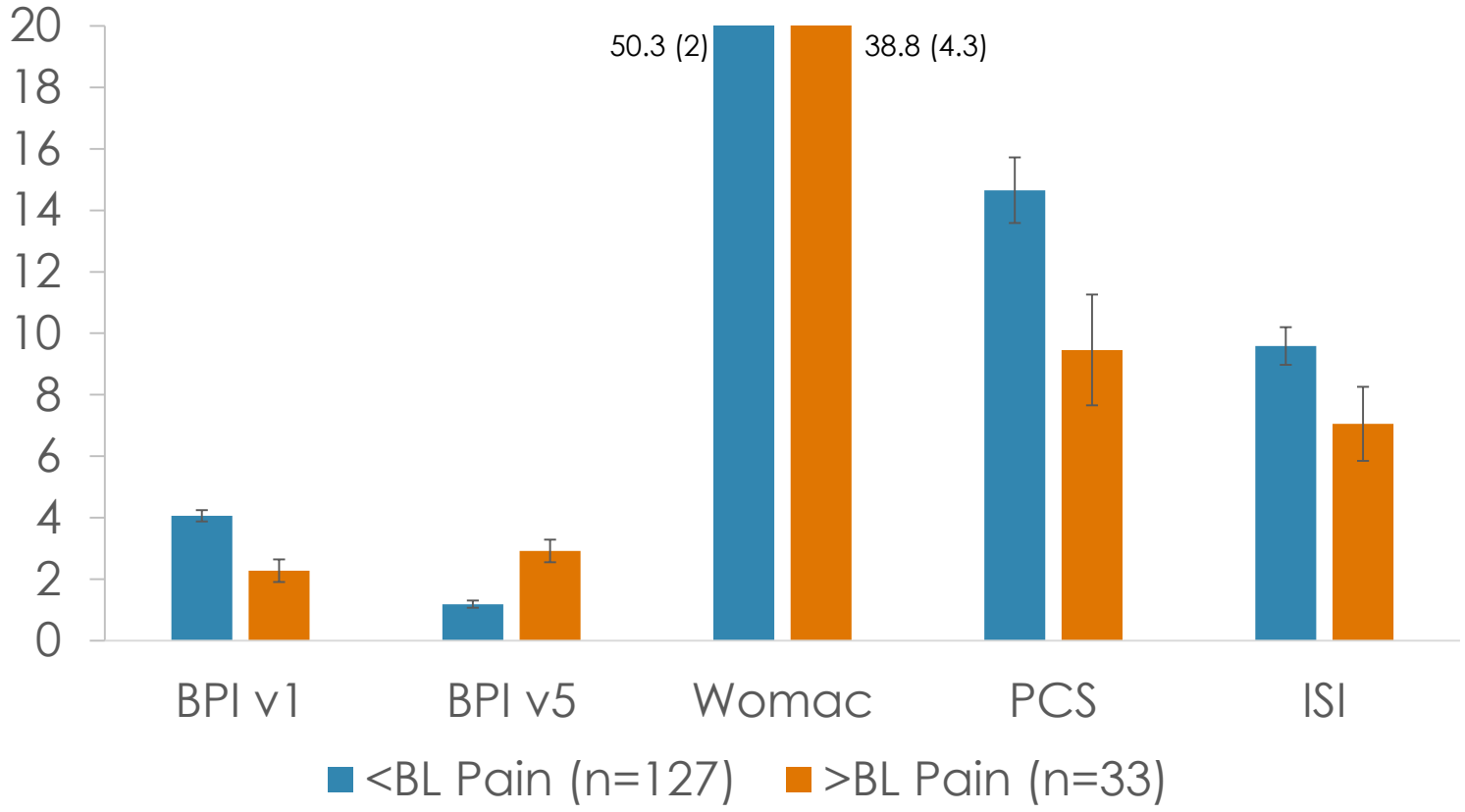
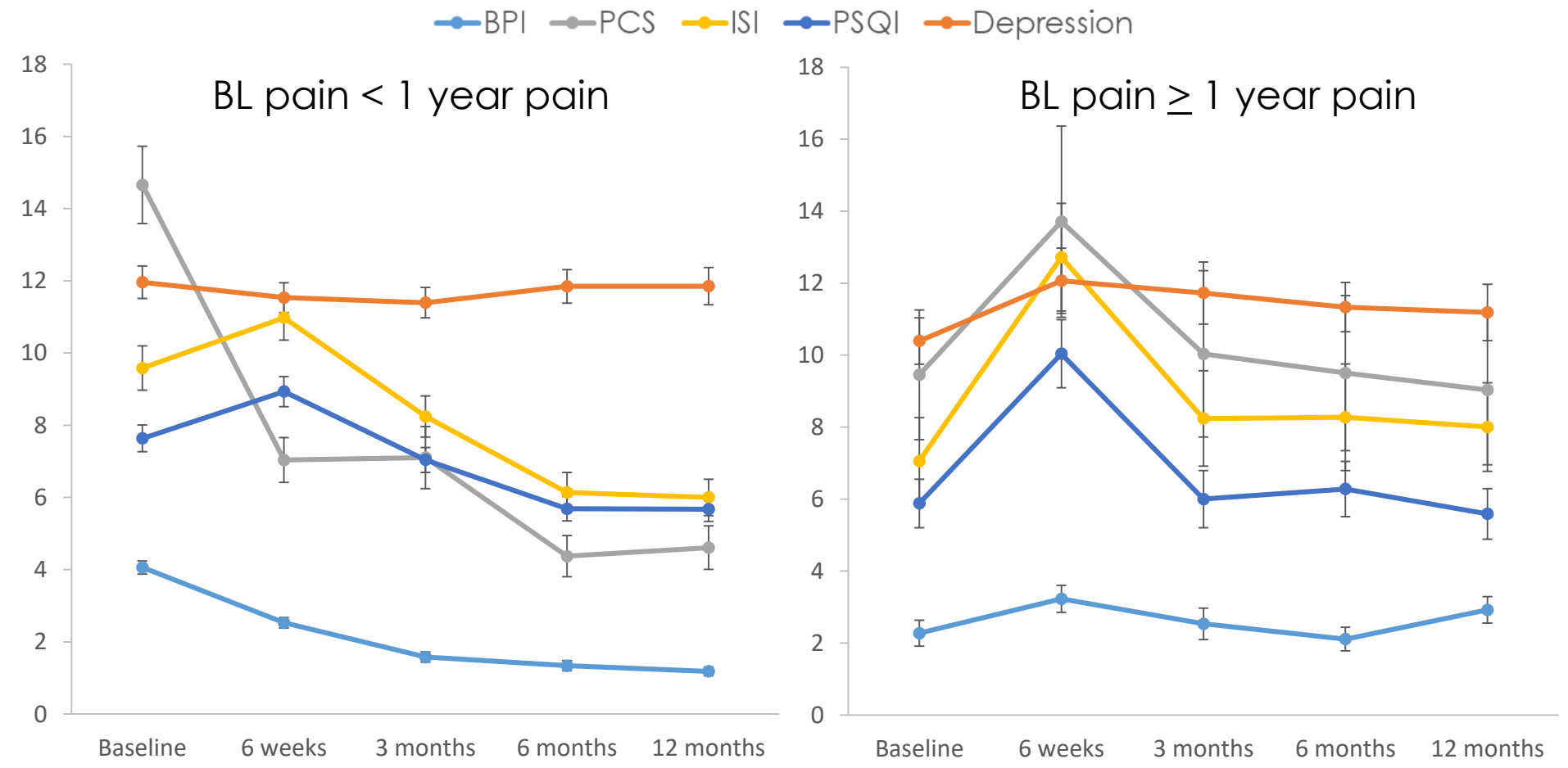


Comparing those whose pain got worse after TKR



Comparing </>BL pain @ 1 year



Chicken and eggs?

- Regardless, seems like there is (or maybe are?) common pathway…
- If you treat pain, will the other symptoms improve?
- If you treat the symptoms, will pain improve?

Catastrophizing Interventions

- Can catastrophizing interventions reduce pain?
- May reduce secondary hyperalgesia
  - Healthy people (Salomons et al., 2014)
- CBT and Lumbar Spinal Fusion
  - No differences at 1 year, CBT group lower disability at 3mo Post (Rolving et al., 2015)

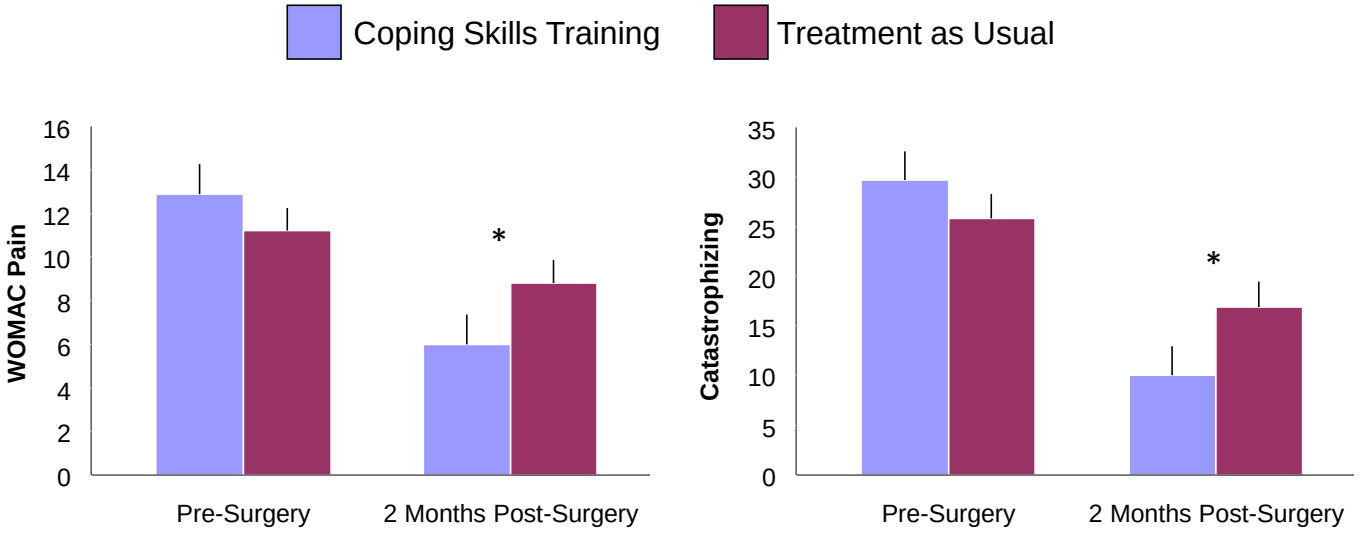
CBT in Surgical Patients

Pain Coping Skills Training for Patients With Elevated Pain Catastrophizing Who Are Scheduled for Knee Arthroplasty: A Quasi-Experimental Study

Daniel L. Riddle, PT, PhD, Francis J. Keefe, PhD, William T. Nay, PhD, Daphne McKee, PhD, David E. Attarian, MD, FACS, Mark P. Jensen, PhD

18 patients, 8 sessions before TKA
Compared to historical controls:

- Tx group reported greater reductions in pain severity and catastrophizing 2 months post-TKA
- Greater improvement in function



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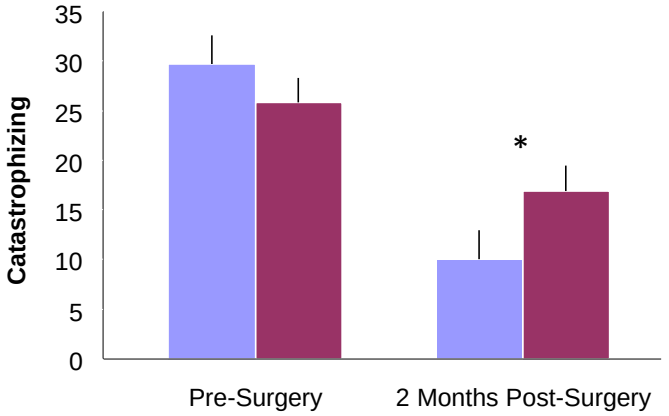
- Greater improvement in function

Coping Skills Training Treatment as Usual

A phase III randomized three-arm trial of physical therapist delivered pain coping skills training for patients with total knee arthroplasty: the KASTPain protocol

Daniel L Riddle[1*], Francis J Keefe[2], Dennis Ang[3], Khaled J[4], Levent Dumenci[5], Mark P Jensen[6], Matthew J Bair[7], Shelby D Reed[8] and Kurt Kroenke[9]



The multisite RCT did not replicate these findings. In 402 patients with high cat, coping skills training did not reduce cat, improve pain or functional outcomes above SOC (Riddle et al., 2019)

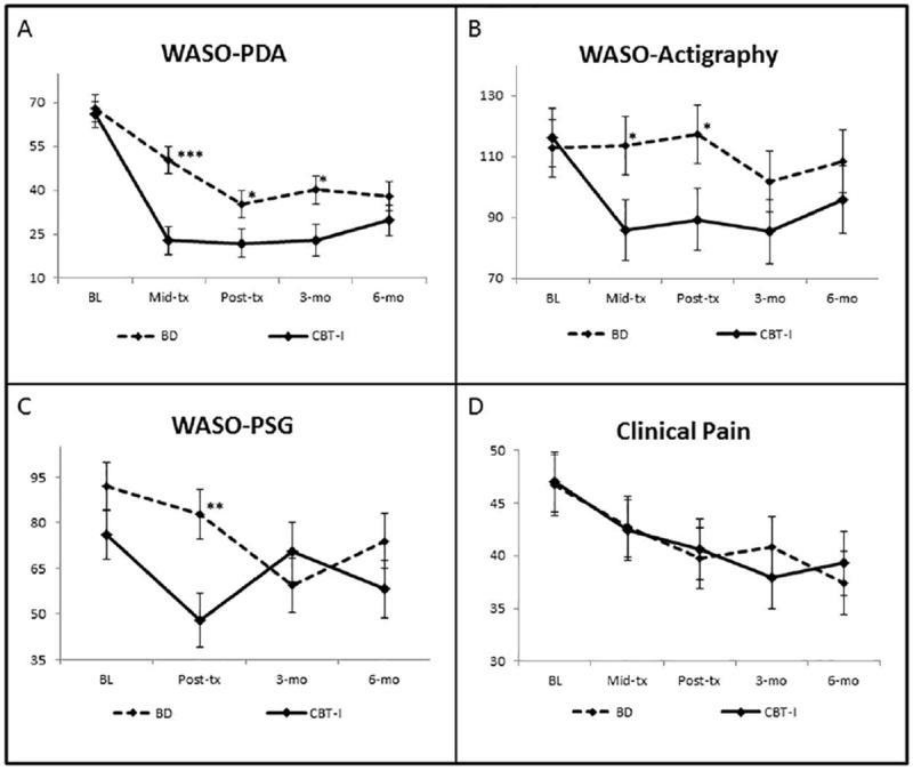
Sleep?

- Strong bidirectional relationship between sleep and pain.

Sleep?

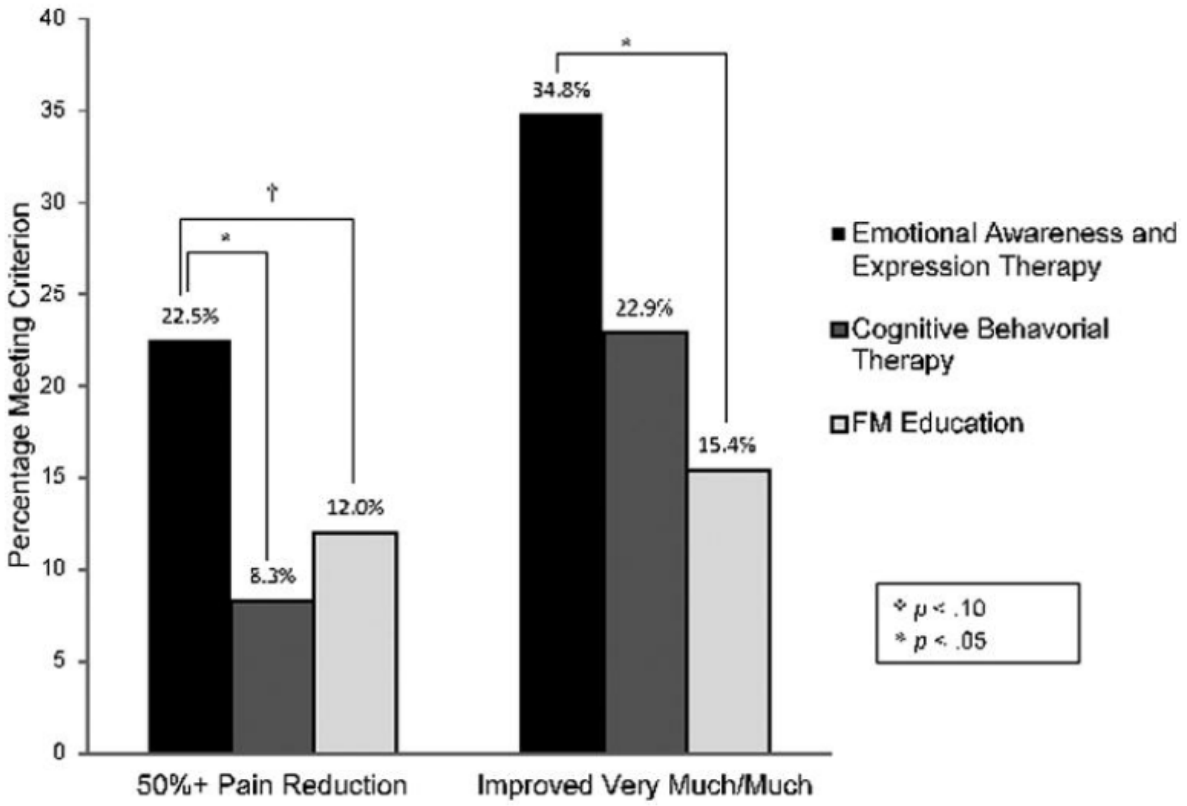
- CBT-I in 100 patients with KOA
- Substantially improved sleep. Reduced pain but not more than behavioral desensitization (control condition)

Smith et al., 2015



Emotional Awareness and Expression Therapy vs. CBT

- No difference between EAET and CBT in pain severity or most other outcomes
- Difference in FM symptoms, WPI and greater prevalence of substantial pain reduction



Implications for SA/CS on treatment

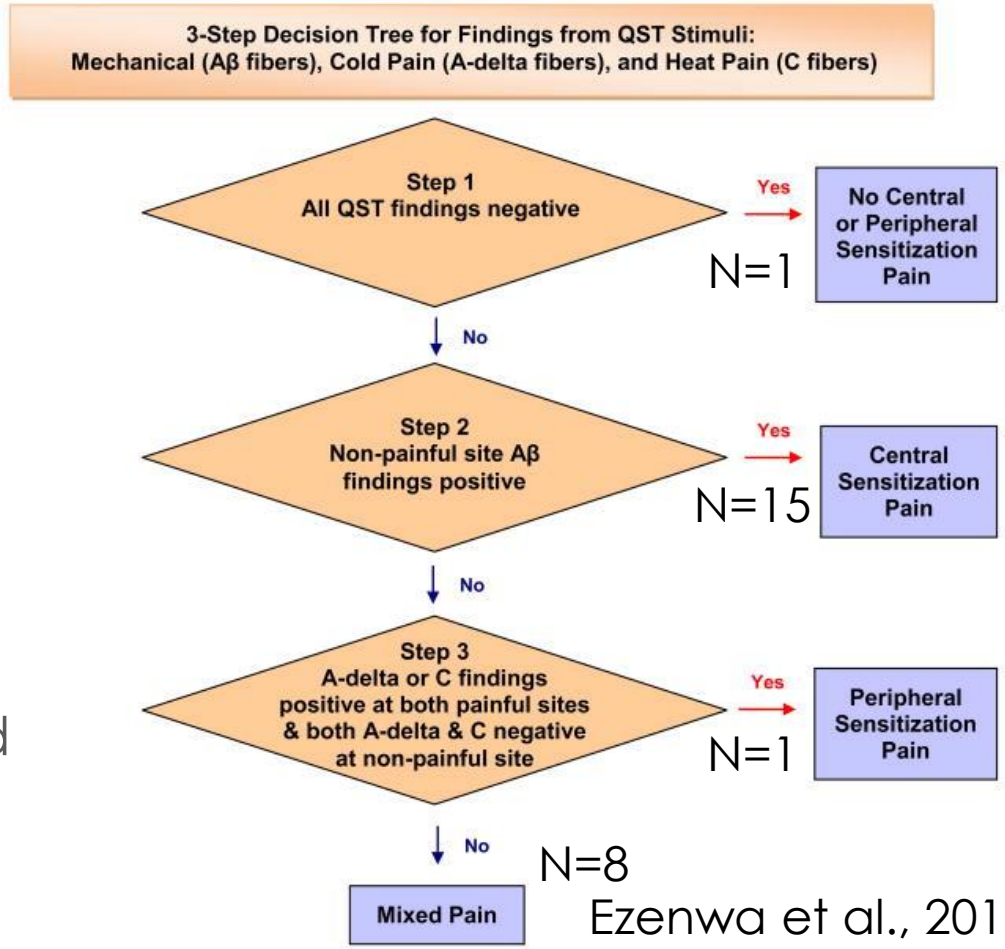
- Recommend a way to:
  - Quantify
  - Consolidate?
  - Interpret
  - Make sense of
- See if they influence treatment?
- Or are influenced by treatment?
- Can/Should subgroup based on them?

How to quantify?

- Many sensory, psychological and behavioral measures
- For QST
  - QST to areas of pain vs. no pain
  - Simple grouping of QST responses – cs relevant vs. not
  - Pain Modulation Profile

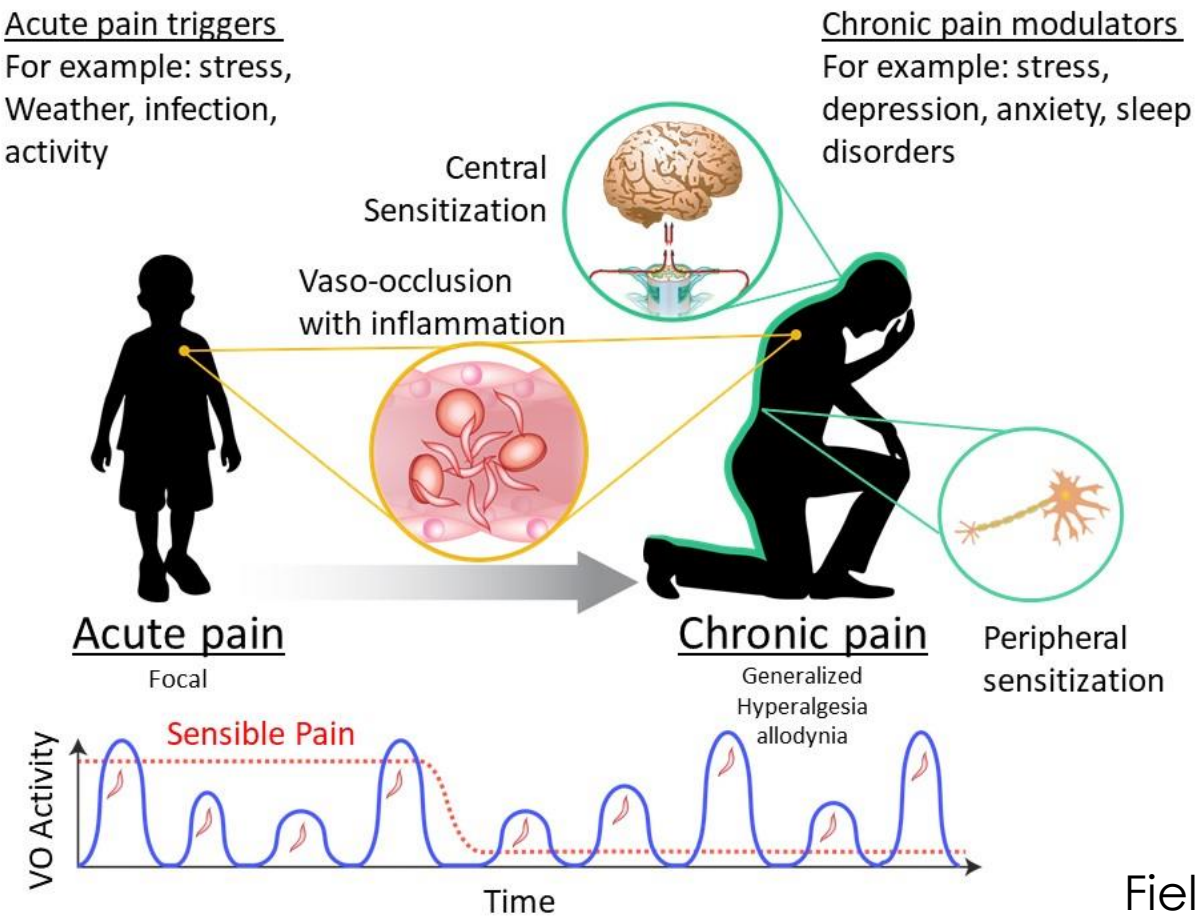
Quantifying amplification

- Thermal thresholds on 3 sites
  - 2 painful
  - 1 not painful site
- Compare to norms
- Determine if sensitivity is widespread or localized over painful sites



Ezenwa et al., 2016

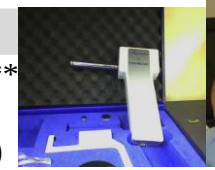
Tangent on SCD

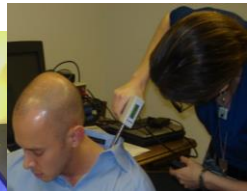


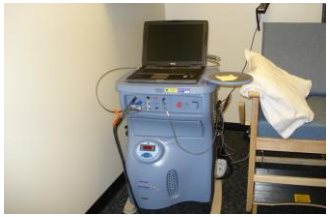
Field et al., 2019

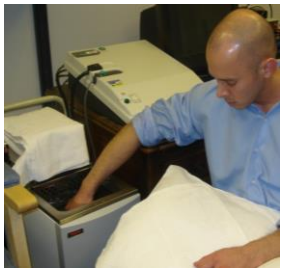
Tangent on SCD

QST Measures	SCD (n = 83)	Healthy Control (n=27)
Thermal Pain in ºCelsius		
Threshold (HPTh)	40.7 (2.8)	41.8 (2.9)
Tolerance (HPTo)	44.0 (2.0)	46.5 (2.2)***
Pressure Pain Threshold in kilopascals (kPa)		
Trapezius	246.1 (99.1)	310.9 (139.9)**
Thumb	301.5 (100.0)	357.0 (112)*
Forearm	239.5 (102.3)	279.1 (117.2)
Quadriceps	520.7 (230.0)	625.5 (252.7)*
Thermal Temporal Summation difference scores		
At Heat Pain Threshold	3.6 (7.2)	2.2 (5.6)
At Threshold + 2ºC	3.8 (8.2)	4.8 (9.7)
At 45ºC	8.0 (14.2)	1.8 (3.5)*
After Sensation Ratings (TTS)	11.8 (17.3)	6.4 (11.8)
Mechanical Temporal Summation difference scores		
128 mN (Probe 5)	12.8 (17.0)	8.3 (13.2)
256 mN (Probe 6)	16.9 (19.1)	10.7 (11.3)
Hot Water Hand Immersion Tests		
Temperature of Hot Water (in ºCelsius)	45.2 (1.4)	48.4 (1.1)***
CPM Difference Trapezius (difference score)	71.4 (64.3)	37.6 (68.9)*
Hot Water Pain Ratings (0-100)	56.0 (26.3)	74.4 (19.1)***
Hot Water Tolerance (in seconds)	47.3(32.4)	32.3 (28.2)*
After Sensation Ratings (hot water; 0-100)	8.7 (12.8)	17.5 (19.9)**









*(p<.05), **(p<.01). Measures are reported as mean (SD). Difference Scores represent the maximal rated pulse (for Thermal Temporal Summation) or following the train of 10 stimuli (for Mechanical Temporal Summation) of the series minus first pulse of the series. CPM: Conditioned Pain Modulation. CPM Difference represents pressure pain thresholds at the trapezius obtained during water immersion of the hand minus baseline trapezius pressure pain thresholds.

Campbell et al., 2016

Quantifying amplification

- Created a high CS group and a low CS group
- Based on:
  - Temporal summation
    - Thermal @ two different temperatures
    - Mechanical
  - After sensations
  - Values were standardized
  - SCD Z values > 1std dev above the healthy control mean counted for each task
  - Those that had >1 std dev on ≥2/4 tasks were deemed 'High CS'

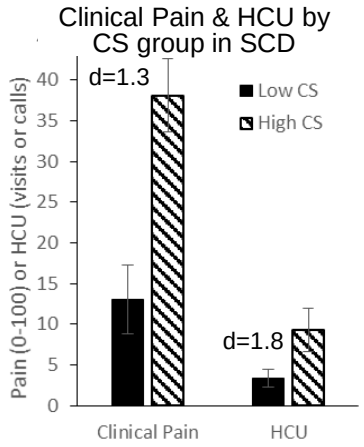
In SCD amplification associated with…

Clinical Variables	Low CS N=17	High CS N=21	p value
Body Mass Index	**24.5 (3.2)**	**27.4 (4.6)**	**0.04***
Systolic Blood Pressure	112.6 (11.0)	116.0 (14.9)	0.44
Diastolic Blood Pressure	69.8 (10.2)	70.5 (10.6)	0.83
Heart Rate	80.3 (11.0)	80.5 (13.1)	0.95
Nicotine Use (smoking)	0% (0)	28.6% (6)	0.42
Genotype			
SS	70.6% (12)	57.1% (12)	0.47
S-Beta zero	5.9% (1)	9.5% (2)	
SC	17.6% (3)	33.3% (7)	
Unknown	5.9% (1)	0% (0)	
History of Acute Chest Syndrome	41.2% (7)	42.9% (9)	0.59
Presence of Avascular Necrosis	29.4% (5)	33.3% (7)	0.54
Taking Hydroxyurea	35.3% (6)	19.0% (4)	-
Taking long-acting opioids	**17.6% (3)**	**57.1% (12)**	**0.013***
Taking short-acting opioids	**52.9% (9)**	**85.7% (18)**	**0.027***

No Other Demographic Differences

In SCD amplification associated with…

Clinical Pain Variables	Low CS (n=17)	High CS (n=21)	p value
Pain			
Pain Severity (BPI)	**0.9 (1.3)**	**2.8 (1.8)**	**0.001*****
Interference (BPI –Extended)	1.5 (2.7)	3.1 (2.4)	0.06
Pain from PDA (0-100; average over 3 months)	n=16	n=20	
Proportion of PDA's completed (total completed days/total possible days)	0.78 (0.2)	0.76 (0.3)	0.80
Non-Crisis Pain	**8.8 (14.5)**	**26.1 (20.5)**	**0.008****
VOC Pain	35.6 (23.4)	52.1 (21.0)	0.11
Average Number of days reporting VOC	**0.09 (0.1)**	**0.23 (0.2)**	**0.044***
Average length of Crises	**0.8 (1.1)**	**1.5 (1.0)**	**0.045***
Number of calls to providers	1.8 (3.0)	4.5 (6.0)	0.11
Number of medical visits	**1.6 (1.8)**	**4.9 (6.1)**	**0.05**
Number of Crises	5.4 (9.2)	12.3 (12.7)	0.08



Clinical pain, some aspects of VOCs and healthcare utilization differ by group

In SCD amplification associated with…

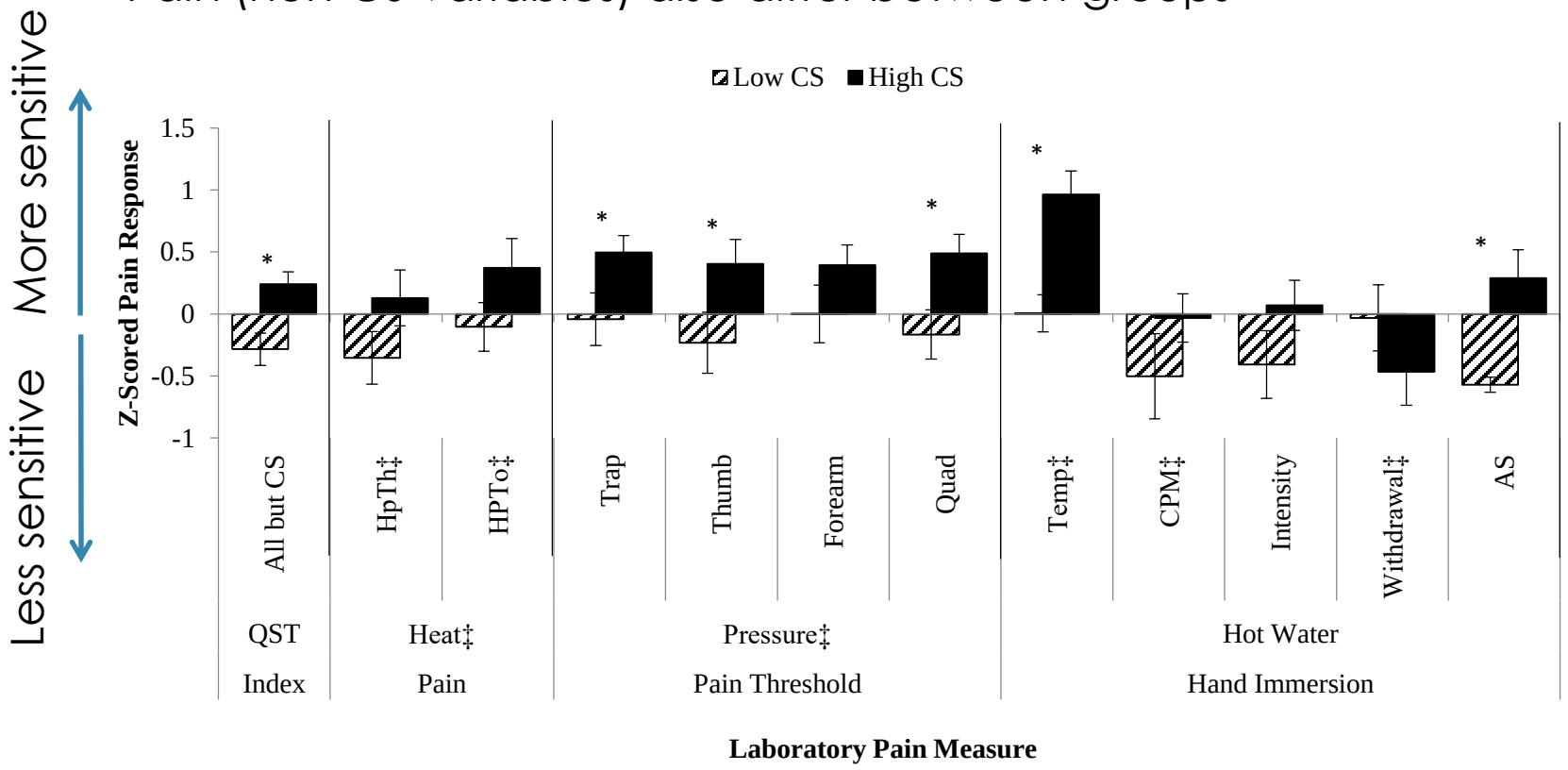
Psychosocial Variables	Low CS	High CS	p value
From Monthly Calls (average over 12 mo)	n=13	n=18	
Catastrophizing	**4.8 (4.7)**	**17.1 (12.5)**	**0.002****
Positive Affect	**7.2 (1.5)**	**5.8 (1.4)**	**0.014***
Negative Affect	**2.6 (1.7)**	**4.1 (1.8)**	**0.026***

In SCD amplification associated with…

Sleep Variables	Low CS (n=17)	High CS (n=21)	p value
PSQI Components			
1. Subjective Sleep Quality	**0.8 (0.5)**	**1.5 (0.8)**	**0.007****
2. Sleep Latency	**0.9 (0.9)**	**1.8 (1.1)**	**0.01***
3. Sleep Duration	**0.5 (0.7)**	**1.3 (1.2)**	**0.01***
4. Habitual Sleep Efficiency	2.6 (1.0)	2.0 (1.3)	0.10
5. Sleep Disturbance	**1.4 (0.7)**	**2.0 (0.7)**	**0.006****
6. Use of Sleep Medications	**0.1 (0.3)**	**1.0 (1.2)**	**0.007****
7. Daytime Dysfunction	0.9 (0.7)	1.3 (0.9)	0.14
Global Score	**7.1 (3.1)**	**10.9 (4.0)**	**0.003****
ISI	**5.4 (6.1)**	**12.5 (8.2)**	**0.005****
Sleep from PDA† (average over 3 months)			
Sleep Efficiency (%)	**89.6% (6.7)**	**77.1% (17.7)**	**0.011***
Wake After Sleep Onset (in minutes)	17.5 (24.3)	35.6 (29.5)	0.057
Sleep Onset Latency (in minutes)	**16.8 (12.9)**	**37.4 (25.1)**	**0.005****
Sleep Duration (in hours)	7.2 (1.2)	7.9 (3.7)	0.53
From Weekly Calls (average over 3 months)			
Sleep Continuity Disturbance	**0.9 (.9)**	**1.9 (1.3)**	**0.029***
Sleep Duration	6.7 (0.9)	6.2 (1.5)	0.34
From Monthly calls (averaged over 12 months)			
Sleep Continuity Disturbance	**1.1 (0.9)**	**2.2 (1.0)**	**0.006****
Sleep Duration	6.5 (1.2)	5.7 (1.1)	0.068

In SCD amplification associated with…

Pain (non CS variables) also differ between groups

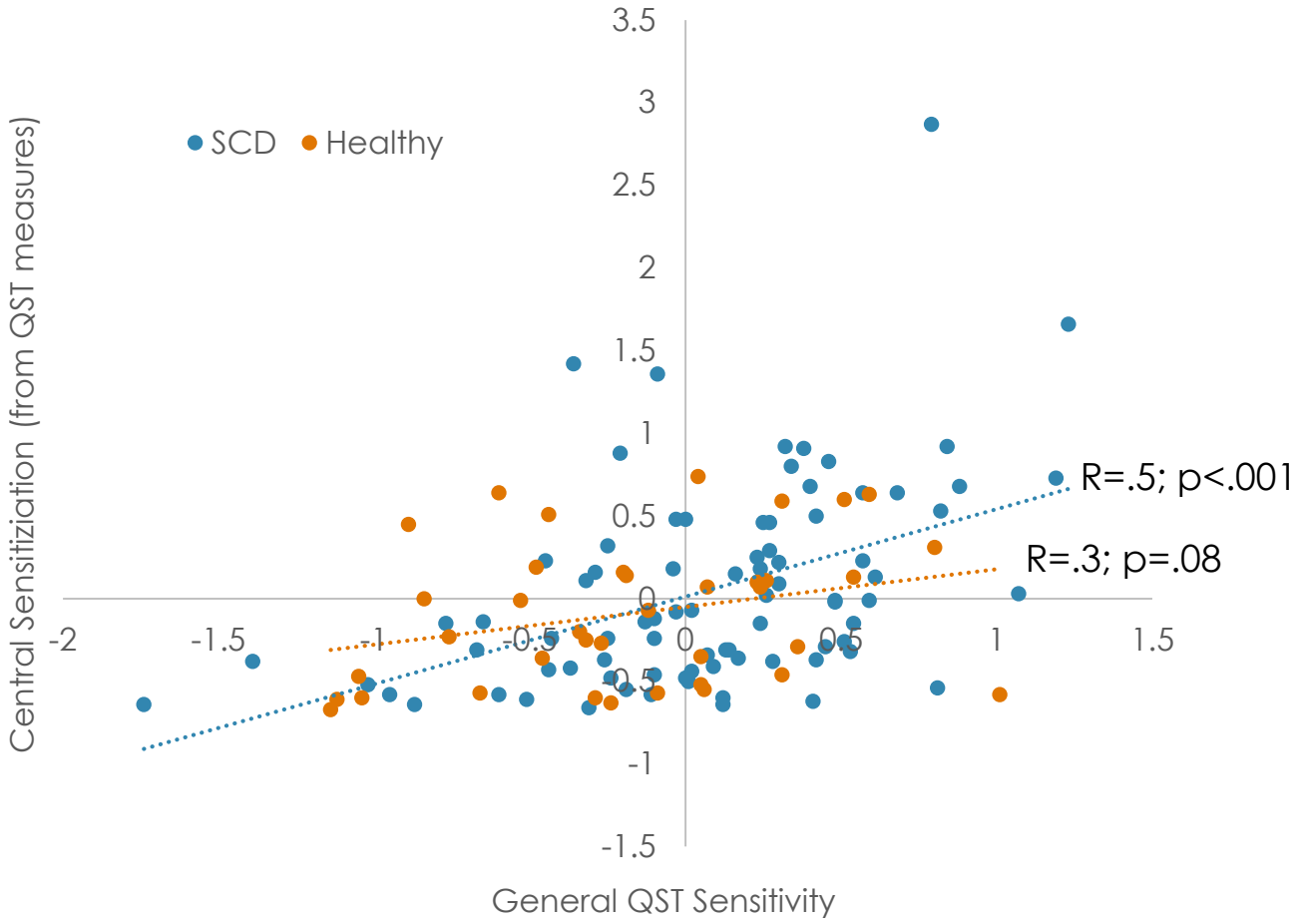


Campbell et al., 2016

Quantifying Amplification

- "Simple" grouping by QST responses
  - Not so simple
- Should we only be assessing CS-related measures?
  - TS
  - AS
  - CPM
- Value in being able to show there isn't widespread/peripheral somatosensory amplification?

Correlation between GS and CS



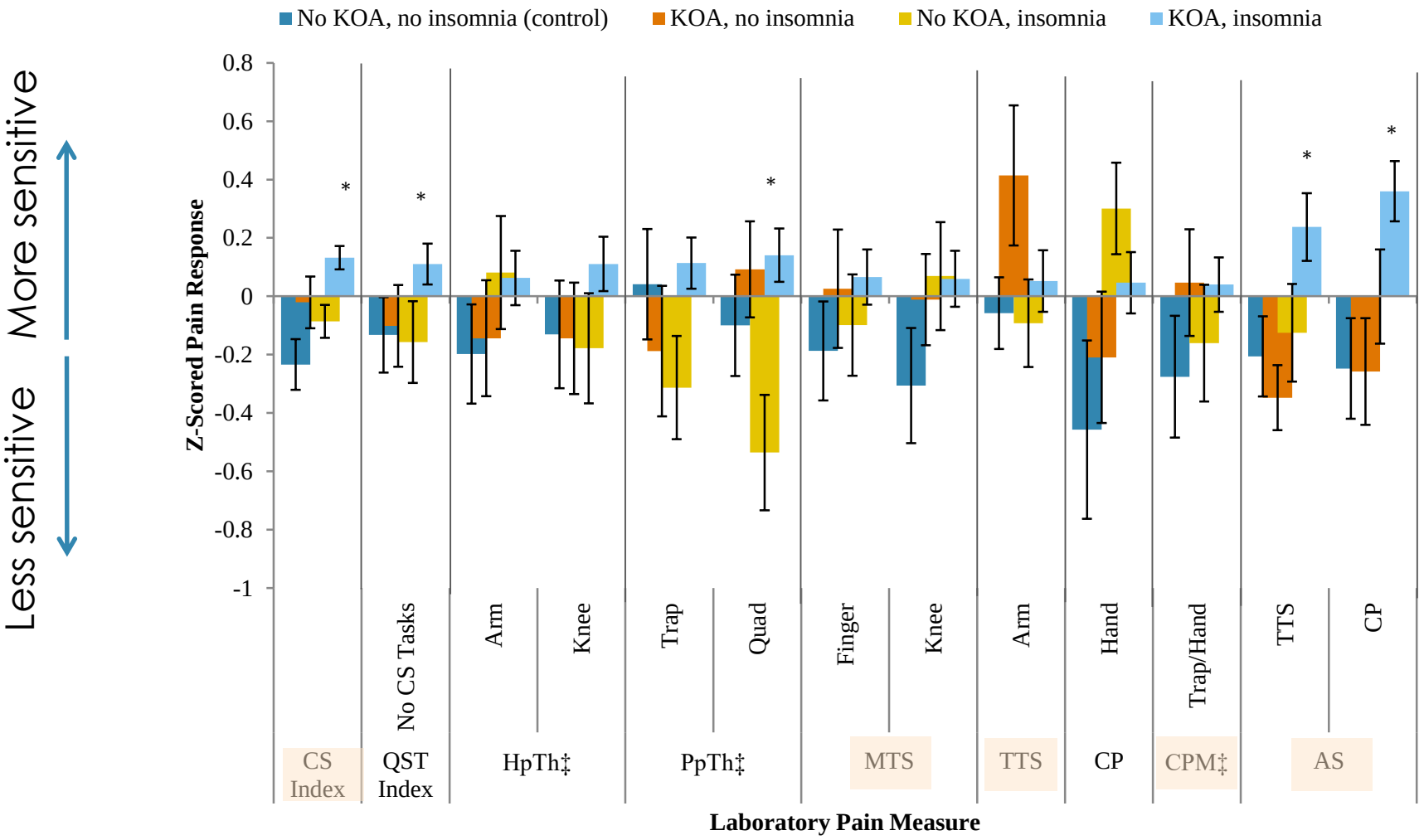
Tangent on SCD

Outcome	No Chronic Opioids Mean (SD)	Chronic Opioid Therapy Mean (SD)	Controlling for Depression	
			Beta	F
Laboratory Indices				
CS Index	**-0.10 (0.4)**	**0.34 (0.8)****	**0.33**	**6.0****
QST Index	0.08 (0.5)	0.02 (0.6)	-0.09	0.4
Diary Indices				
Non-Crisis Pain	**10.3 (14.1)**	**34.5 (15.7)*****	**0.50**	**21.9*****
Proportion of Days in VOC	**11.9% (16.4)**	**29.0% (26.3)****	**0.30**	**7.3***
Crisis Pain	**41.0 (21.0)**	**60.6 (11.4)*****	**0.40**	**8.9****

Something special about these more 'CS' measures than simple somatosensory amplification

Carroll et al., 2016

Quantifying Amplification

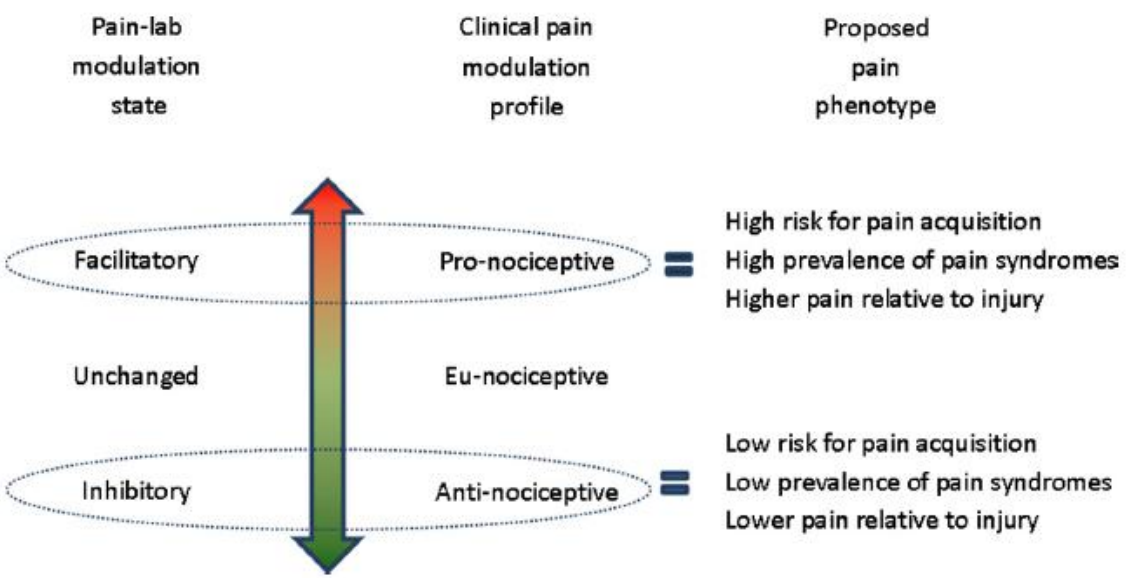


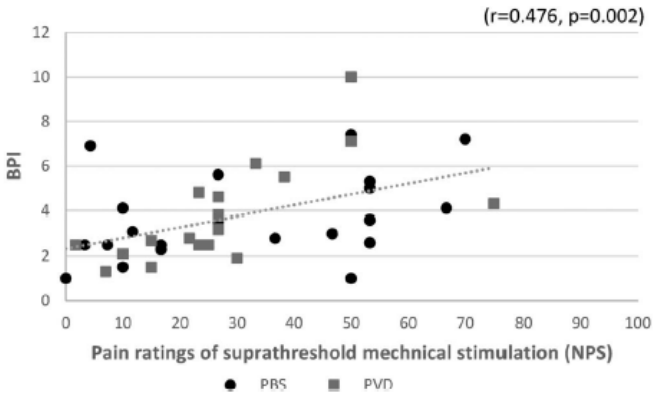
Quantifying Amplification

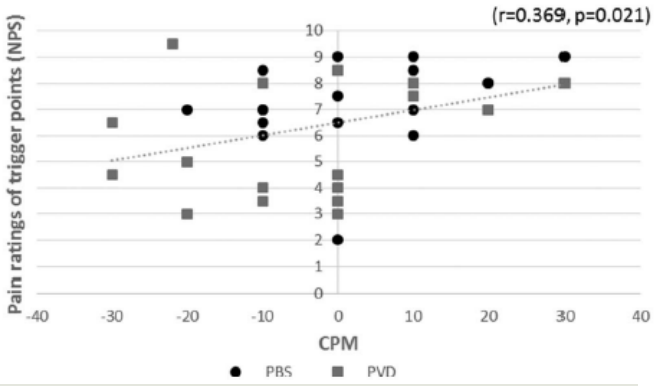
- Pain Modulation Profile

Pain modulation profile and pain therapy: Between pro- and antinociception

David Yarnitsky [a,b,*], Michal Granot [c], Yelena Granovsky [a,b]



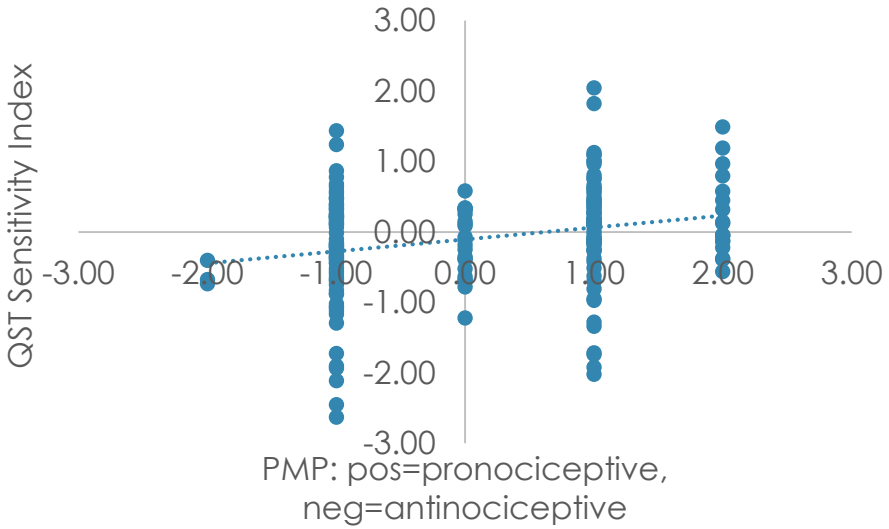




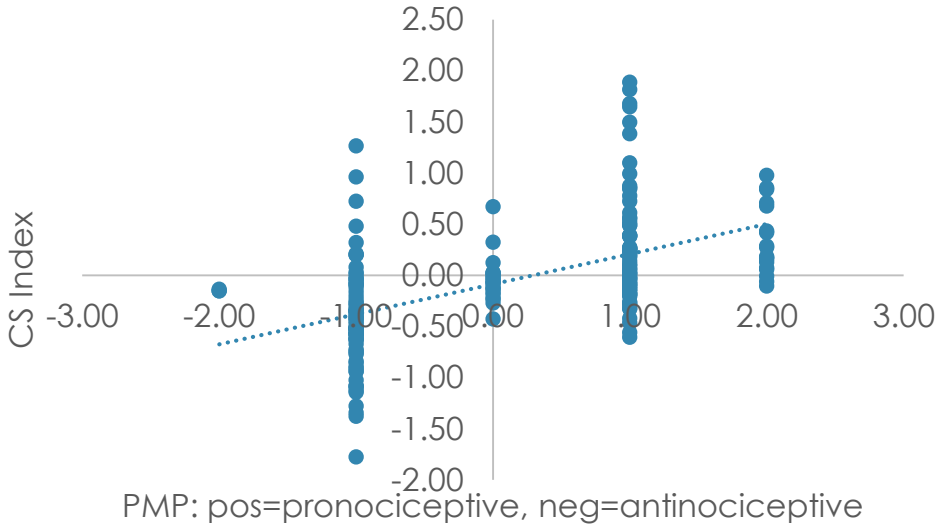
- Grinberg et al., 2017

How do these different methods relate?

- In TKR…



R=.25; p=.001



R=.54; p<.001

How are they related to WPI/SS?

Correlations

		bpi_severity.v1: Mean of Worst, Least, Average, and Current Pain Qs	wpi_sum.v1: WPI Sum	ss_sum.v1: Symptom Severity Sum	Nociceptive profile - pos=pronociceptive, neg=antinociceptive	QSTsens_indexNocsbasic.v1	CS_TtsMtsShsAsCMP.v1
bpi_severity.v1: Mean of Worst, Least, Average, and Current Pain Qs	Pearson Correlation	1	.242**	.387**	.056	.187*	.080
	Sig. (2-tailed)		.000	.000	.489	.016	.285
	N	209	209	172	155	164	179
wpi_sum.v1: WPI Sum	Pearson Correlation	.242**	1	.348**	.058	.201**	-.015
	Sig. (2-tailed)	.000		.000	.431	.005	.823
	N	209	246	197	184	197	214
ss_sum.v1: Symptom Severity Sum	Pearson Correlation	.387**	.348**	1	-.019	.181*	-.015
	Sig. (2-tailed)	.000	.000		.819	.023	.844
	N	172	197	197	150	158	171
Nociceptive profile - pos=pronociceptive, neg=antinociceptive	Pearson Correlation	.056	.058	-.019	1	.245**	.542**
	Sig. (2-tailed)	.489	.431	.819		.001	.000
	N	155	184	150	184	180	184
QSTsens_indexNocsbasic.v1	Pearson Correlation	.187*	.201**	.181*	.245**	1	.337**
	Sig. (2-tailed)	.016	.005	.023	.001		.000
	N	164	197	158	180	198	198
CS_TtsMtsShsAsCMP.v1	Pearson Correlation	.080	-.015	-.015	.542**	.337**	1
	Sig. (2-tailed)	.285	.823	.844	.000	.000	
	N	179	214	171	184	198	215

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

What about patient selection?

- Can/Should we continue to rule out those with more than 'our' dx of choice?
  - Easier to recruit, more generalizable and more meaningful to include other pain conditions
  - Likely something different about those with a more narrow pain. Select and subtype of patients included in clinical trial if exclude those with widespread or multiple locations.
  - Chronic widespread pain vs. regional – differ from those with focused pain.
  - Will the FDA/funding agencies allow/accept that?

What about patient selection?

- Several reviews have summarized the utility of QST in advancing personal medicine
- Should we subgroup or classify participants?
  - Forecasting analgesic benefit

Amplification associated with analgesia

Forecasting analgesic benefit:

- Lidocaine
- Lamotrigine
- Pregabalin
- Duloxetine
- Oxycodone
- Oxcarbazepine
- Placebo analgesia
- Morphine
- Mexiletine
- NSAIDs

Pain Medicine

Pain Medicine 2014; 15: 61–72
Wiley Periodicals, Inc.

PSYCHOLOGY, PSYCHIATRY & BRAIN NEUROSCIENCE SECTION

Review Article

Can Quantitative Sensory Testing Move Us Closer to Mechanism-Based Pain Management?

Cruz-Almeida & Fillingim, 2014

Pain. 2016 September ; 157(9): 1851–1871. doi:10.1097/j.pain.0000000000000602.

Patient phenotyping in clinical trials of chronic pain treatments: IMMPACT recommendations

Edwards et al., 2016

Can quantitative sensory testing predict responses to analgesic treatment?

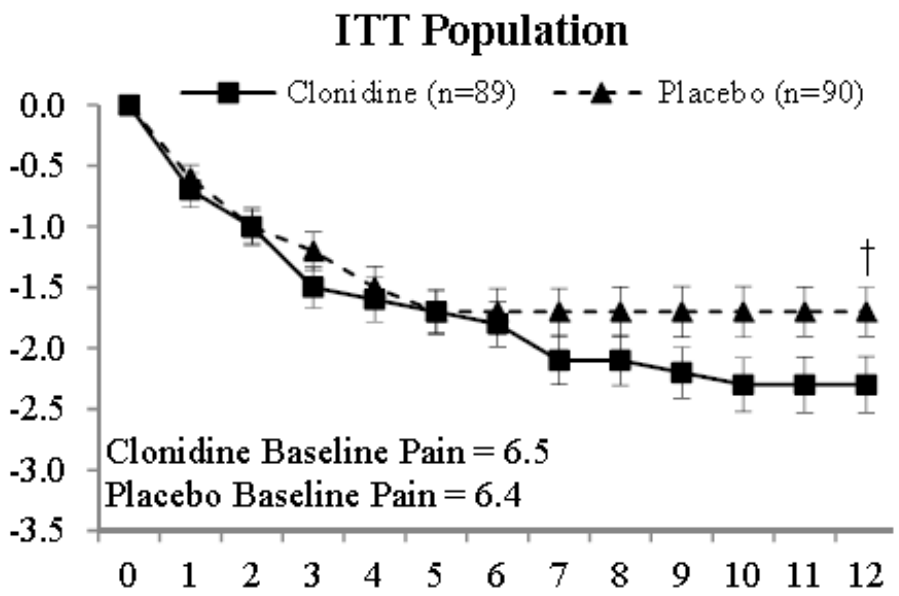
K. Grosen[1], I.W.D. Fischer[2,3], A.E. Olesen[2], A.M. Drewes[2,4]

2013

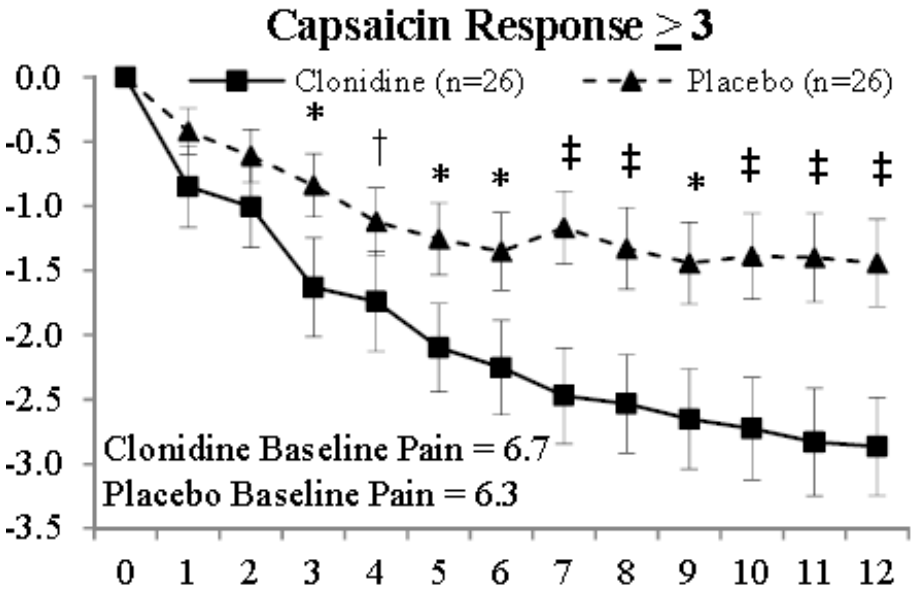
What about patient selection?

- Premature?
- Several reviews have summarized the utility of QST in advancing personal medicine
  - Forecasting analgesic benefit
  - Quantifying sensory function and its potential value in tailoring treatment
    - Multidisciplinary Pain Treatment
    - Spinal Cord Stimulation – CPM/TTS predicted efficacy
    - Topical Pain Treatments

Clonidine Efficacy by Capsaicin Response



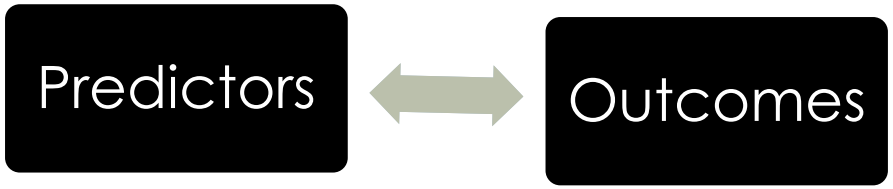
Functional Nociceptors?



Campbell et al., 2012

Implications?

- QST
  - Temporal Summation
  - Conditioned Pain Modulation
  - Static Tests?
- Psychological
  - Mood (anxiety/depression/affect)
  - Catastrophizing
  - Stress
  - Fatigue
  - Trauma history
  - Kinesiophobia
  - Fear of pain
- Behavioral
  - Sleep
  - Diet?
  - Exercise?
  - Smoking?
- Social
  - Support?
  - Solicitousness?
  - Work
  - SES
  - Demographic
  - HCU
- Physical
  - Pain Severity
  - # Painful Sites (pain at each?)
  - QST
  - Widespread 'fibromyalgianess'
  - Disability
- Function!



What outcomes?

- BPI
- What is being rated?
- One ring to rule them all?

3. **Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

4. **Please rate your pain by marking the box beside the number that best describes your pain at its least in the last 24 hours.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

5. **Please rate your pain by marking the box beside the number that best describes your pain on the average.**

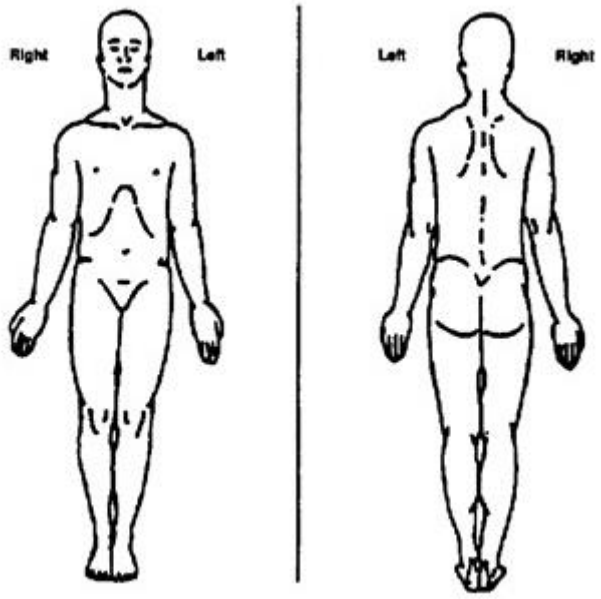
☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine

6. **Please rate your pain by marking the box beside the number that tells how much pain you have right now.**

☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10

No Pain — Pain As Bad As You Can Imagine



How would we put it all together if asked these for EVERY marked site?

What outcomes?

- Focus on function (thriving/functional/bedridden)
  - Functional capacity evaluation in the laboratory?
  - Wear a pedometer for x time? *
  - Use a disease specific measure of function?

Turk et al., 2016

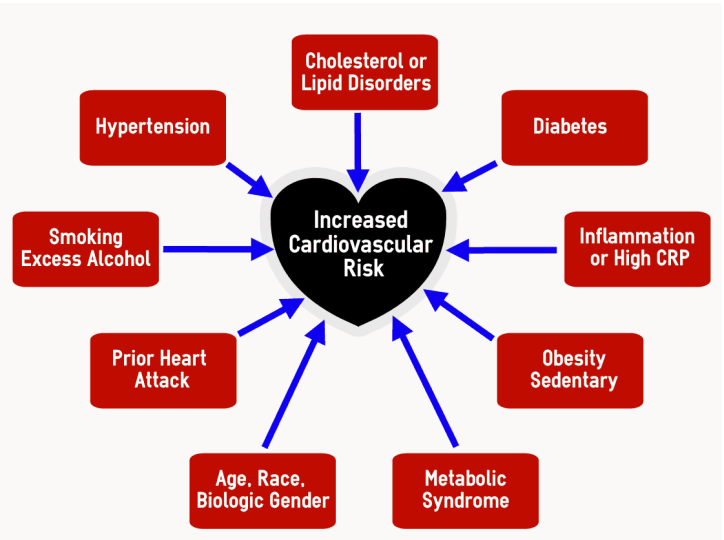
- Psych outcomes/behavior?

Constellation of vulnerability

- If CS/SSA is a continuum, how do we measure/define/describe that?
- Does the distribution of those factors matter?
- Is there a meaningful way to put it all together and measure movement on factors?

Constellation of vulnerability

- Take a note from the cardiovascular literature?



Blood pressure (mmHg)						
Other risk factors, OD or disease		Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥180 or DBP ≥110
No other risk factor	Risk level	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
	Follow up visits /year	0	0	2	2	3.5
1-2 risk factors	Risk level	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
	Follow up visits /year	3.5	3.5	2	2	3.5
3 or more risk factors, MS, OD or Diabetes	Risk level	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
	Follow up visits /year	3.5	3.5	3.5	3.5	3.5
Established CV or renal disease	Risk level	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk
	Follow up visits /year	3.5	3.5	3.5	3.5	3.5

Is there a way to put it all together?

Baseline Factors						
Clinical Pain	Function	Lab Markers	SSA	SPACE		
Pain Sites and Severity	Impact: Q's, wearables, function testing	Biomarkers (inflammation/tender point counts)/CS (TS, CPM, AS)	GS (questionnaire(s), static QST	Behavioral Factors (smoking, sleep, vigor…)	Psychological Factors (cat, depression, anxiety	Cognitive issues
Head						
Foot						
Joints						
Jaw						
Back						
Knee						

Is there a way to put it all together?

Active

Clinical Pain	Function	Lab Markers	SSA	SPACE		
Pain Sites and Severity	Impact: Q's, wearables, function testing	Biomarkers (inflammation/tenderpoint counts)/CS (TS, CPM, AS)	GS (questionnaire(s), static QST	Behavioral Factors (smoking, sleep, vigor…)	Psychological Factors (cat, depression, anxiety	Cognitive issues
Head						
Foot						
Joints						
Jaw						
Back						
Knee						

Placebo

Clinical Pain	Function	Lab Markers	SSA	SPACE		
Pain Sites and Severity	Impact: Q's, wearables, function testing	Biomarkers (inflammation/tenderpoint counts)/CS (TS, CPM, AS)	GS (questionnaire(s), static QST	Behavioral Factors (smoking, sleep, vigor…)	Psychological Factors (cat, depression, anxiety	Cognitive issues
Head						
Foot						
Joints						
Jaw						
Back						
Knee						

Summary

- Subgrouping patients?
  - Treat them differently?
- What predictors/what outcomes?
  - Both CS/GS measures?
- Should we recommend using QST?
  - Which tasks?
  - How should we present those data?
  - Should it be reduced?
- Is there a better way to show the variables impacted by treatment?

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